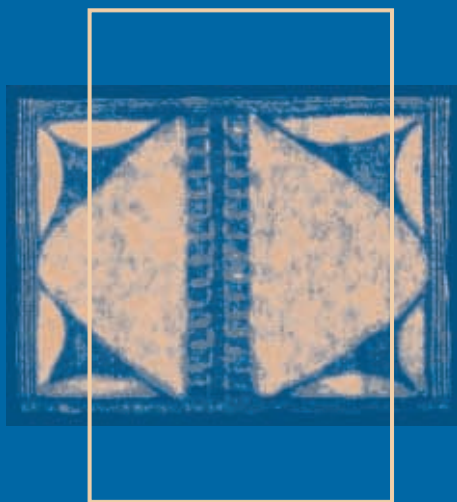


TREATMENT *of* TUBERCULOSIS



GUIDELINES *for* NATIONAL PROGRAMMES



WORLD HEALTH ORGANIZATION

TREATMENT OF TUBERCULOSIS: GUIDELINES FOR NATIONAL PROGRAMMES

THIRD EDITION



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First edition, 1993
Second edition, 1997
Third edition, 2003

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PREFACE

The World Health Organization's Stop TB Department has prepared this third edition of Treatment of tuberculosis: guidelines for national programmes with the help of the International Union Against Tuberculosis and Lung Disease and experts worldwide. The aim is to give practical guidance to national tuberculosis programmes (NTPs) and the medical profession in the effective management of TB. The principles of treatment, as set out in the two previous editions of the book, remain the same. The purpose of this revision is to update the guidelines in the light of the experience gained in assisting NTPs and to present information on HIV-related TB and multidrug-resistant TB (MDR-TB) and chronic cases. This book is intended primarily for use where 95% of the global TB burden exists. Guidelines for high-income, low-incidence countries, while following the same principles, include recommendations that may not be appropriate for most high-incidence countries where resources for TB control are often limited.

The most cost-effective public health measure for the control of tuberculosis is the identification and cure of infectious TB cases, i.e. patients with smear-positive pulmonary TB. Nevertheless, NTPs provide for the identification and cure of all patients with TB. These guidelines cover the treatment of patients, both adults and children, with smear-positive pulmonary TB, smear-negative pulmonary TB and extrapulmonary TB.

Treatment of TB is the cornerstone of any NTP. The modern treatment strategy is based on standardized short-course chemotherapy regimens and proper case management to ensure completion of treatment and cure. Standardized treatment is a component of the TB control policy package, set out in WHO's expanded framework for effective tuberculosis control¹, and of the internationally recommended strategy for TB control known as "DOTS". Success of the treatment strategy depends on commitment to the policy package in its entirety. The emphasis is on placing the patient at the centre of TB control activities, the health system being responsible for facilitating access to treatment and ensuring drug intake. The DOTS strategy provides the TB patient with all the necessary requirements for cure. These revised guidelines focus on the technical and managerial aspects of treatment.

The objectives of the revised guidelines are:

- to describe the global TB burden and the strategy and framework for effective TB control;
- to describe standardized treatment regimens according to TB case definitions and categories, including chronic and MDR-TB cases;
- to describe the monitoring of individual patients and how to ensure their adherence to treatment;

¹ *An expanded DOTS framework for effective tuberculosis control*. Geneva, World Health Organization, 2002 (document WHO/CDS/TB/2002.297).

- to describe the special considerations in treating HIV-infected TB patients;
- to provide information on TB drug supply in the context of national pharmaceutical policies and essential drugs programmes.

This new edition is intended for use by NTPs as a tool for setting national policy for TB treatment and training staff, as a reference book for medical and nursing schools, and for clinicians working in the public and private sectors. The guidelines are aimed primarily at NTP managers, policy-makers in ministries of health, nongovernmental organizations and donor agencies, but clinical health workers and teachers, and students in medical and nursing schools will also find them useful.

Jong Wook Lee
Director, Stop TB

FOREWORD TO THE SECOND EDITION

There will be a warm welcome for this second edition of the Guidelines. The first edition in 1993 was most valuable and has been extensively used. Since its publication much more experience of National Tuberculosis Control Programmes in a wide variety of countries has accumulated. It is appropriate therefore that the Guidelines should be reviewed.

The initial approach to that review was to explore whether the previous recommendations could be simplified. After wide consultation it became clear that there were considerable variations between countries both in circumstances and in resources. It was therefore decided that the Guidelines should have some degree of flexibility. For several aspects of a control programme there should be reliable alternatives. Each national programme can choose the treatment regimens and modes of application most appropriate to its own circumstances.

One of the important activities of a national tuberculosis programme is finding solutions to problems. For example, how can a programme in a country with limited resources implement directly observed treatment in a rural area with poor infrastructure? It is essential to evaluate proposed methods of implementing directly observed treatment. Wider adoption of a particular proposed method depends on proven success of that method in carefully identified demonstration sites.

The key treatment principle of direct observation of treatment remains the same whichever method of implementation is chosen. For all smear-positive cases, directly observed treatment is always recommended in the initial phase of treatment and when the continuation phase contains rifampicin. The results of this approach are the following: high sputum smear conversion rates at the end of the initial phase; high cure rates; decreased prevalence of chronic excretors of tubercle bacilli; decreased transmission of infection; prevention of drug-resistance.

The writers of the Guidelines are to be congratulated on their success on presenting the key principles with clarity and relative simplicity. The text presents much practical advice based on experience in many different national programmes. It takes into account the tragic impact of the HIV pandemic on the individual patient, on the epidemiology of tuberculosis and on the necessary modification of programmes.

With the global explosion of HIV, and in some countries much ill-informed and chaotic treatment of tuberculosis, the world is threatened with an untreatable epidemic of multi-drug resistant tuberculosis. The only way to prevent it is to ensure that the principles outlined in this booklet are universally applied, both in government programmes and in private practice. We must all make every effort to ensure that this vital objective is indeed achieved. Time is not on our side. The need is urgent. These Guidelines must have the widest possible distribution.

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ABBREVIATIONS AND ACRONYMS

AFB	<i>Acid-fast bacilli</i>
AIDS	<i>Acquired immunodeficiency syndrome</i>
CXR	<i>Chest X-ray</i>
DOT	<i>Directly observed treatment</i>
DOTS	<i>Internationally recommended strategy for TB control</i>
E	<i>Ethambutol</i>
EPTB	<i>Extrapulmonary tuberculosis</i>
FDC	<i>Fixed-dose combination</i>
GDF	<i>Global Drug Facility</i>
GLC	<i>Green Light Committee</i>
H	<i>Isoniazid</i>
HAART	<i>Highly active antiretroviral therapy</i>
HIV	<i>Human immunodeficiency virus</i>
IUATLD	<i>International Union Against Tuberculosis and Lung Disease</i>
MDR-TB	<i>Multidrug-resistant TB (resistance to at least rifampicin and isoniazid)</i>
NNRTI	<i>Non-nucleoside reverse transcriptase inhibitor</i>
NRTI	<i>Nucleoside reverse transcriptase inhibitor</i>
NTP	<i>National tuberculosis programme</i>
PHC	<i>Primary health care</i>
PI	<i>Protease inhibitor</i>
PTB	<i>Pulmonary tuberculosis</i>
R	<i>Rifampicin</i>
RTI	<i>Reverse transcriptase inhibitor</i>
S	<i>Streptomycin</i>
SMX	<i>Sulfamethoxazole</i>
STB	<i>Stop TB Department</i>
T	<i>Thioacetazone</i>
TB	<i>Tuberculosis</i>
TMP	<i>Trimethoprim</i>
TB/HIV	<i>HIV-related TB</i>
UNAIDS	<i>Joint United Nations Programme on HIV/AIDS</i>
USAID	<i>United States Agency for International Development</i>
WHO	<i>World Health Organization</i>
Z	<i>Pyrazinamide</i>



I INTRODUCTION

I.1 Global epidemiology and burden of disease

Nearly one-third of the global population, i.e. two billion people, is infected with *Mycobacterium tuberculosis* and at risk of developing the disease. More than eight million people develop active tuberculosis (TB) every year, and about two million die (1).

More than 90% of global TB cases and deaths occur in the developing world, where 75% of cases are in the most economically productive age group (15-54 years). There, an adult with TB loses on average three to four months of work time. This results in the loss of 20-30% of annual household income and, if the patient dies of TB, an average of 15 years of lost income (2). In addition to the devastating economic costs, TB imposes indirect negative consequences - children leave school because of their parents' tuberculosis, and women are abandoned by their families as a result of their disease.

Coinfection with the human immunodeficiency virus (HIV) significantly increases the risk of developing TB (3). Countries with a high prevalence of HIV, particularly those in sub-Saharan Africa, have witnessed a profound increase in the number of TB cases, with reported incidence rates increasing two- or three-fold in the 1990s (4).

At the same time, multidrug resistance, which is caused by poorly managed TB treatment, is a growing problem of serious concern in many countries around the world (5).

I.2 Reasons for the global TB burden

The main reasons for the increasing burden of TB globally are:

- poverty and the widening gap between rich and poor in various populations, e.g. developing countries, disenfranchised urban populations in developed countries;
- neglect of the disease (inadequate case detection, diagnosis and cure);
- collapse of the health infrastructure in countries experiencing severe economic crisis or civil unrest;
- the impact of the HIV pandemic.

I.3 Global TB control is possible through the DOTS strategy

The essential services needed to control TB, based on diagnosis and treatment of infectious cases and incorporating the essential management tools, were

developed and packaged as the DOTS strategy in the early 1990s (section 2.2). DOTS has been promoted as a global strategy since the mid-1990s.

Countries applying DOTS on a wide scale have witnessed remarkable results. Transmission has declined in several countries; in Peru, for example, incidence has dropped by approximately 6% per year over the past decade (6). Mortality has fallen: in China, some 30 000 deaths have been averted each year in districts implementing DOTS (7). Drug resistance has decreased: in New York in the 1990s, the prevalence of TB drug resistance fell by 75% following intensive interventions to improve patient management and reduce TB transmission (8).

Properly applied TB chemotherapy is effective in curing infectious cases, thereby interrupting the chain of transmission. The best prevention of TB is therefore the cure of infectious TB cases. The World Bank recognizes the DOTS strategy as one of the most cost-effective health interventions, and recommends that effective TB treatment be a part of the essential clinical services package available in primary health care (PHC) (9). Governments are responsible for ensuring the provision of effective TB control through the DOTS strategy.

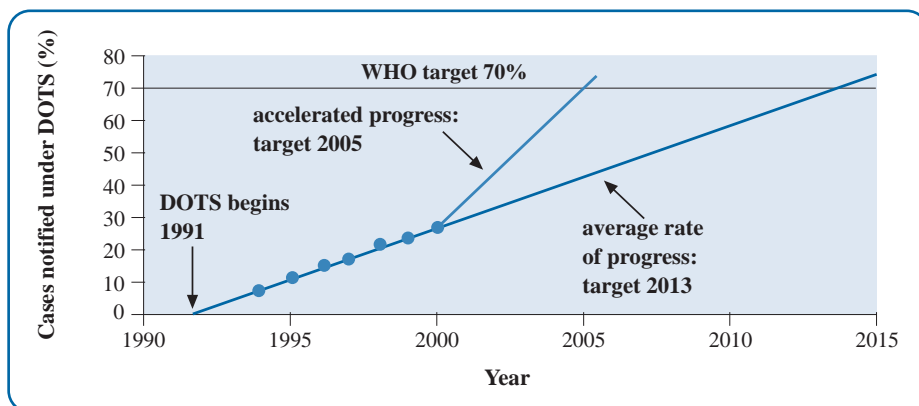
The need to improve tools for diagnosis, treatment and prevention of TB to make TB control more effective is well recognized. Initiatives have been launched to develop new diagnostics, drugs and vaccines, and the international community has started to increase investment in TB research (10).

1.4 Slow progress to control TB

Despite widespread acceptance of the principles of DOTS, most developing countries have been unable to expand DOTS as rapidly as needed and have failed to achieve the global targets of detecting 70% of infectious cases and curing 85% of those detected. The main constraints to rapid expansion were identified by an Ad Hoc Committee on the Tuberculosis Epidemic in 1998 as lack of political commitment, insufficient and ineffective use of financial resources, neglect of human resource development, poor health system organization and TB managerial capability, poor quality and irregular supply of antituberculosis drugs, and lack of information (11).

The number of countries adopting DOTS has increased dramatically over the past decade, from a handful in 1990 to 148 in 2002. At the end of 2000, however, only 27% of infectious pulmonary TB cases were treated under DOTS programmes. With current efforts to control TB, it is expected that the global target for detecting and treating efficiently 70% of cases worldwide will be reached only by 2013 (Figure 1.1). Accelerating DOTS expansion to achieve the target by 2005 - to which all countries have recently committed as part of the Amsterdam declaration in March 2000 - will have a profound health and socioeconomic impact, saving 18 million lives by 2010 and 48 million new cases by 2020 (12). This "fast track" to DOTS will also mitigate the impact of HIV and reduce the prevalence of drug resistance.

Figure 1.1 Progress towards the target of 70% case definition, for 22 high TB burden countries, given the current and accelerated rate of progress.



1.5 Rationale for updating the guidelines

The first edition of the treatment guidelines was published in 1993. The second edition in 1997 included significant changes to facilitate implementation and adaptation to different national conditions.

Recent years have provided additional national experience in the implementation of the DOTS strategy and the effectiveness of selected regimens. There is also increased managerial and financial national capacity to implement regimens for chronic and drug-resistant tuberculosis, for which guidelines were published in 1996. This justifies a new edition of the treatment guidelines that includes:

- updated case definitions and treatment recommendations;
- a chapter on regimens for chronic and drug-resistant cases;
- alternatives for management of cases who fail Category I treatment;
- details on enablers for direct observation and successful treatment, such as integration into general health facilities, decentralization, patient's choice of treatment supporter, community care, fixed-dose combination tablets, patient boxes and blister packs;
- management of extrapulmonary and childhood TB;
- expansion of the chapter on TB in persons infected with HIV.

As before, this new edition is intended primarily for national tuberculosis programme (NTP) managers as a tool for setting national policy for TB treatment and training staff, as a guide for medical and nursing schools, and for clinicians working in the public and private sectors.

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STRATEGY AND FRAMEWORK FOR EFFECTIVE TUBERCULOSIS CONTROL

2.1 Objectives of chapter

This chapter describes WHO's expanded DOTS strategy and framework for effective TB control.

2.2 Background

The World Health Organization declared TB a global emergency in 1993 in recognition of its growing importance as a public health problem. Governments in many high-burden countries have neglected TB control in the past. Tuberculosis programmes have failed to achieve high detection and cure rates for infectious (smear-positive) patients. Besides poverty, population growth and migration, and an increase in the number of TB cases attributable to the HIV epidemic in some countries, the persistence of TB has been chiefly due to:

- failure to ensure accessible diagnosis and treatment services, including directly observed therapy;
- inadequate treatment regimens and failure to use standardized treatment regimens;
- lack of supervision and an information management system for the rigorous evaluation of treatment outcomes of TB patients;
- misguided policies for health sector reform, with cuts in health care budgets and resultant reduction in financial support to peripheral health services.

In response to this situation, a new framework for effective TB control was developed and a global strategy called DOTS was introduced (Box 2.1).

Box 2.1 Five components of the DOTS strategy

- 1 Sustained political commitment.
- 2 Access to quality-assured sputum microscopy.
- 3 Standardized short-course chemotherapy for all cases of TB under proper case management conditions, including direct observation of treatment.
- 4 Uninterrupted supply of quality-assured drugs.
- 5 Recording and reporting system enabling outcome assessment of all patients and assessment of overall programme performance.

The organizational principles of the DOTS strategy are:

- availability of a decentralized diagnostic and treatment network based on existing health facilities and integrated with PHC;
- good programme management based on accountability and supervision of health care workers;
- an evaluation system of case-finding and cohort analysis of treatment outcomes.

The WHO framework for effective TB control includes the objectives and targets, DOTS strategy, a policy package, key operations for implementation, and indicators to measure progress.

2.3 Objectives and targets

The objectives of an NTP are to reduce TB mortality, morbidity and disease transmission, while preventing the development of drug resistance.

The main intervention for TB control is standardized short-course chemotherapy provided under direct observation - at least during the initial phase of treatment - for all identified smear-positive TB cases, the main sources of infection. (Chronic and drug-resistant cases are considered in Chapter 5.)

The global targets for TB control, adopted by the World Health Assembly, are to cure 85% of newly detected cases of sputum smear-positive TB and to detect 70% of the estimated incidence of sputum smear-positive TB.¹ National TB programmes achieving at least an 85% cure rate and 70% detection of patients with sputum smear-positive pulmonary TB have the following impact:

- rapid reduction of TB mortality, prevalence and transmission, and gradual reduction of TB incidence;
- less acquired drug resistance, thus making future treatment of TB easier and more affordable.

National TB programmes achieving low cure rates reduce mortality but produce more cases of sputum smear-positive treatment failure and default, thereby increasing prevalence, transmission and acquired drug-resistant TB. Case detection should be increased only when an NTP has achieved a high cure rate throughout the country.

**An effective national tuberculosis programme has
a high cure rate,
a low level of acquired drug resistance,
and ultimately a high case detection rate.**

¹ Resolution WHA44.8 of the Forty-fourth World Health Assembly, Geneva, World Health Organization, 1991 (WHA44/1991/REC/1), and Resolution WHA46.36 of the Forty-sixth World Health Assembly, Geneva, World Health Organization, 1993.

2.4 Policy package for TB control: the expanded DOTS framework

In order to achieve the targets for TB control in the face of new challenges, TB programmes need to be strengthened significantly.

- General public health services need to enhance their capacity to sustain and expand DOTS implementation without compromising the quality of case detection and treatment.
- Community involvement in TB care and a patient-centred approach need emphasis and promotion to improve both access to and use of health services.
- Collaboration and synergy among the public, private and voluntary sectors are essential to ensure accessible and quality-assured TB diagnosis and treatment, under the guidance of national health authorities.
- The growing impact of HIV on TB incidence and mortality calls for new partnerships and approaches.
- A surge in drug-resistant TB requires effective implementation of the DOTS strategy as well as measures to cure existing multidrug-resistant TB (MDR-TB) cases.

The expanded DOTS framework reinforces the five essential components of the DOTS strategy:

- 1 **Sustained political commitment** to increase human and financial resources and make TB control a nationwide priority integral to the national health system.
- 2 **Access to quality-assured TB sputum microscopy** for case detection among persons presenting with, or found through screening to have, symptoms of TB (most importantly, prolonged cough). Special attention is necessary for case detection among HIV-infected people and other high-risk groups, such as household contacts of infectious cases and people in institutions.
- 3 **Standardized short-course chemotherapy for all cases of TB under proper case management conditions, including direct observation of treatment.** Proper case management conditions imply technically sound and socially supportive treatment services.
- 4 **Uninterrupted supply of quality-assured drugs** with reliable drug procurement and distribution systems.
- 5 **Recording and reporting system enabling outcome assessment of all patients and assessment of overall programme performance.** This is the basis for systematic programme monitoring and correction of identified problems.

2.5 Key operations for DOTS implementation

The seven key operations for implementation of the DOTS strategy are:

- 1 Establish a national tuberculosis programme with a strong central unit.
- 2 Prepare a programme development plan and a programme manual, and establish the recording and reporting system allowing cohort analysis of treatment outcomes.
- 3 Plan and initiate a training programme.
- 4 Set up a microscopy services network in close contact with PHC services and subject to regular quality control to ensure that detection and cure of smear-positive TB cases remain a priority, through effective decentralization of diagnosis.
- 5 Organize treatment services within the PHC system where directly observed short-course chemotherapy is given priority.
- 6 Secure a regular supply of drugs and diagnostic material.
- 7 Design and implement a plan of supervision of key operations at the intermediate and district level.

Other important operations essential to strengthen and sustain DOTS implementation include information, education, communication and social mobilization, involving private and voluntary health care providers, economic analysis and financial planning, and operational research.

2.6 Indicators

The main indicators used to measure progress in implementation of DOTS are the availability of an NTP manual consistent with the DOTS strategy, the number of administrative areas in the country implementing the new TB control strategy, the cure and success rate in new smear-positive cases, and the case detection rate.

Suggestions for further reading

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3 CASE DEFINITION

3.1 Objectives of chapter

The diagnosis of tuberculosis refers to the recognition of an active case, i.e. a patient with symptomatic disease due to *M. tuberculosis*. Beyond the diagnosis of TB disease, the type of TB case should also be defined to allow appropriate treatment to be given and the outcome of treatment evaluated. This applies to all TB patients, both adults and children. This chapter explains the purpose, importance, determinants and uses of case definition.

3.2 Why case definition?

The purposes of case definition are:

- proper patient registration and case notification;
- prioritized treatment of sputum smear-positive cases, the main sources of infection in the community;
- allocation of cases to appropriate standardized treatment regimens;
- evaluation of the proportion of cases according to site, bacteriology and treatment history;
- cohort analysis of treatment outcomes.

3.3 Why match standardized treatment regimen to diagnostic category?

The reasons for matching standardized treatment regimen to diagnostic category are:

- to avoid under-treatment of previously treated cases and therefore to prevent acquired resistance;
- to maximize cost-effective use of resources and to minimize side-effects for patients by avoiding unnecessary over-treatment.

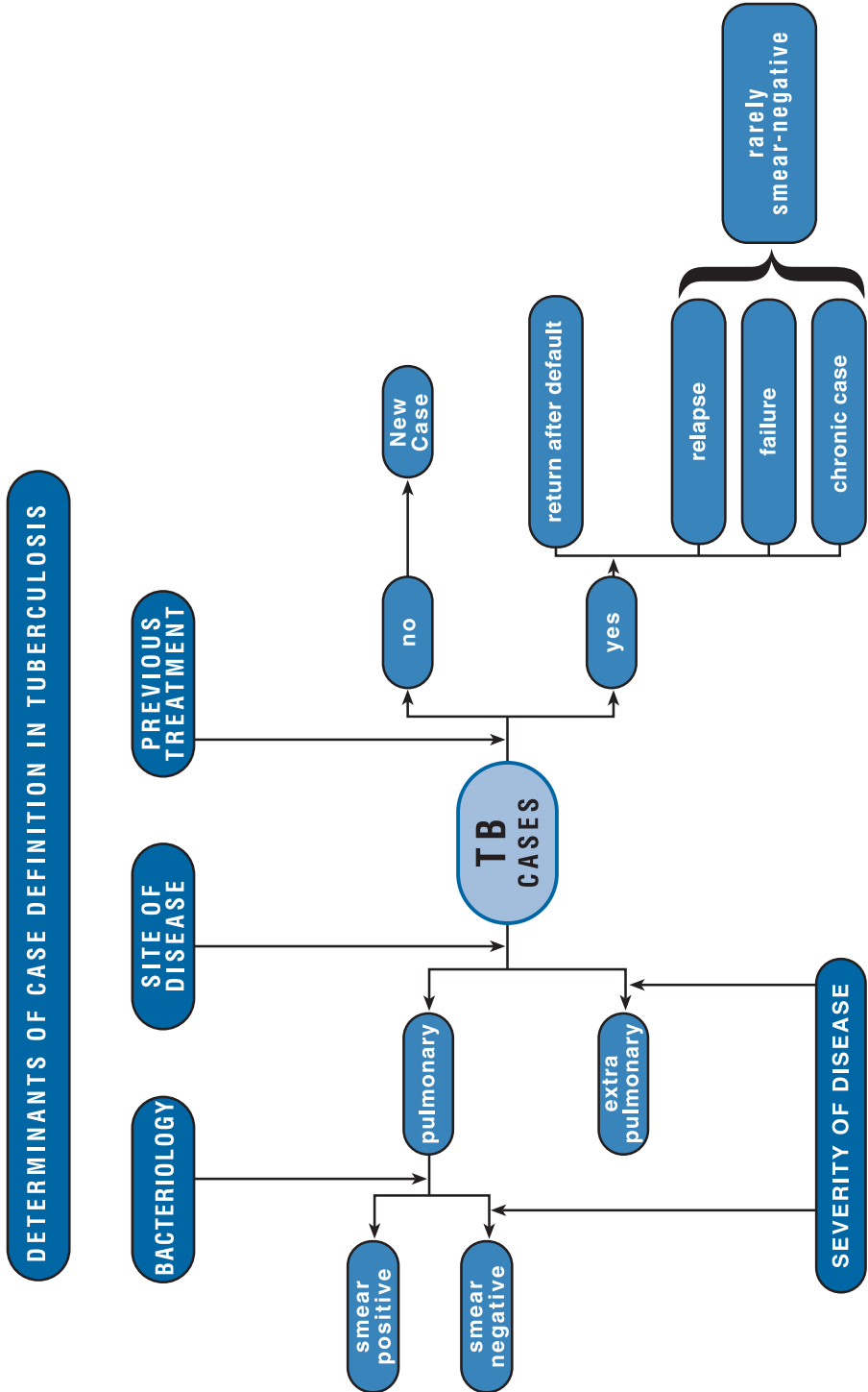
3.4 What determines case definition?

The four determinants of case definition are:

- Site of TB disease.
- Bacteriology (result of sputum smear).
- Severity of TB disease.
- History of previous treatment of TB.

Figure 3.1 summarizes the determinants of case definition.

Figure 3.1: Determinants of case definitions in tuberculosis



3.5 Case definitions

- **Tuberculosis suspect.** Any person who presents with symptoms or signs suggestive of TB, in particular cough of long duration (more than 2 weeks)
- **Case of tuberculosis.** A patient in whom TB has been bacteriologically confirmed or diagnosed by a clinician.

Note. Any person given treatment for tuberculosis should be recorded as a case. Incomplete "trial" tuberculosis treatment should not be given as a method for diagnosis.

- **Definite case of tuberculosis.** A patient with positive culture for the *Mycobacterium tuberculosis* complex. (In countries where culture is not routinely available, a patient with two sputum smears positive for acid-fast bacilli (AFB) is also considered a "definite" case.)

3.5.1 Site of TB disease (pulmonary and extrapulmonary)

In general, recommended treatment regimens are similar irrespective of site. The importance of defining site is primarily for recording and reporting purposes.

Pulmonary tuberculosis (PTB) refers to disease involving the lung parenchyma. Therefore tuberculous intrathoracic lymphadenopathy (mediastinal and/or hilar) or tuberculous pleural effusion, without radiographic abnormalities in the lungs, constitutes a case of extrapulmonary TB. A patient with both pulmonary and extrapulmonary TB should be classified as a case of pulmonary TB.¹

Extrapulmonary tuberculosis (EPTB) refers to tuberculosis of organs other than the lungs, e.g. pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges. Diagnosis should be based on one culture-positive specimen, or histological or strong clinical evidence consistent with active EPTB, followed by a decision by a clinician to treat with a full course of tuberculosis chemotherapy. The case definition of an extrapulmonary TB case with several sites affected depends on the site representing the most severe form of disease.

3.5.2 Bacteriology (result of sputum smear) in pulmonary TB

Defining the smear result in pulmonary cases is important to:

- identify smear-positive cases, because they are the most infectious cases and usually have higher mortality;
- record, report and evaluate programme performance (smear-positive cases are the cases for which bacteriological monitoring of treatment progress is most practicable).

¹ Miliary tuberculosis is classified as pulmonary TB because there are lesions in the lungs.

Although culture is useful to diagnose TB, it is not as important as smear microscopy for TB control. Culture facilities are not universally available and the results take several weeks or months, which is too late to monitor progress. Smear-negative, culture-positive patients are less infectious and, except in immunodepressed individuals, have fewer bacilli. In general, the treatment regimens are the same for culture-positive and culture-negative patients.

The flow chart in Annex 1 shows the recommended diagnostic procedure for suspected pulmonary TB. The following definitions are used:

- Pulmonary tuberculosis, sputum smear-positive (PTB+)
 - a. two or more initial sputum smear examinations positive for AFB, or
 - b. one sputum smear examination positive for AFB plus radiographic abnormalities consistent with active PTB as determined by a clinician, or
 - c. one sputum smear positive for AFB plus sputum culture positive for *M. tuberculosis*.
- Pulmonary tuberculosis, sputum smear-negative (PTB-)

Case of PTB that does not meet the above definition for smear-positive TB. This group includes cases without smear result, which should be exceptional in adults but are relatively more frequent in children.

Note. In keeping with good clinical and public health practice, diagnostic criteria for PTB-should include:

- at least three sputum specimens negative for AFB, and
- radiographic abnormalities consistent with active PTB, and
- no response to a course of broad-spectrum antibiotics, and
- decision by a clinician to treat with a full course of antituberculosis chemotherapy.

Under programme conditions, when microscopy laboratory services are available and diagnostic criteria are properly applied, PTB smear-positive cases represent at least 65% of the total of PTB cases in adults, and 50% or more of all TB cases. Note that these proportions may be lower in high HIV-incidence populations.

It is apparent from the above definitions that in the absence of culture, standard chest radiography is necessary to document cases of smear-negative PTB. Fluoroscopy examination results are not acceptable as documented evidence of PTB.

3.5.3 Severity of TB disease

Bacillary load, extent of disease and anatomical site are considerations in determining TB disease severity and therefore the appropriate treatment. Involvement of an anatomical site results in classification as severe disease if there is a significant acute threat to life (e.g. pericardial TB), a risk of subsequent severe handicap (e.g. spinal TB), or both (e.g. meningeal TB).

Miliary, disseminated TB is considered to be severe. The following forms of EPTB are classified as severe: meningeal, pericardial, peritoneal, bilateral or extensive pleural effusive, spinal, intestinal, genitourinary. Lymph node, pleural effusion (unilateral), bone (excluding spine), peripheral joint and skin tuberculosis are classified as less severe.

3.5.4 *History of previous treatment: category of patient for registration on diagnosis*

In order to identify those patients at increased risk of acquired drug resistance and to prescribe appropriate treatment, a case should be defined according to whether or not the patient has previously received TB treatment. This distinction is also essential for epidemiological monitoring of the TB epidemic at regional and country level.

The following definitions are used:

- **New.** A patient who has never had treatment for TB or who has taken antituberculosis drugs for less than 1 month.
- **Relapse.** A patient previously treated for TB who has been declared cured or treatment completed, and is diagnosed with bacteriologically positive (smear or culture) tuberculosis.
- **Treatment after failure.** A patient who is started on a re-treatment regimen after having failed previous treatment.
- **Treatment after default.** A patient who returns to treatment, positive bacteriologically, following interruption of treatment for 2 months or more.
- **Transfer in.** A patient who has been transferred from another TB register to continue treatment.
- **Other.** All cases that do not fit the above definitions. This group includes **chronic case**, a patient who is sputum-positive at the end of a re-treatment regimen.

Note. Smear-negative pulmonary and extrapulmonary cases may also be relapses, failures, returns after default or chronic cases. This should, however, be a rare event, supported by pathological or bacteriological evidence (culture).

Suggestions for further reading

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4 STANDARDIZED TREATMENT REGIMEN

4.1 Objectives of chapter

This chapter describes the recommended standardized treatment regimens for the different categories of TB cases.

4.2 Aims of treatment

The aims of treatment of TB are:

- to cure the patient of TB;
- to prevent death from active TB or its late effects;
- to prevent relapse of TB;
- to decrease transmission of TB to others;
- to prevent the development of acquired drug resistance.

It is vital to achieve these aims while preventing the selection of resistant bacilli in infectious patients.

4.3 Essential antituberculosis drugs

There are three main properties of antituberculosis drugs: bactericidal activity, sterilizing activity and the ability to prevent resistance. The essential antituberculosis drugs possess these properties to different extents. Isoniazid and rifampicin are the most powerful bactericidal drugs, active against all populations of TB bacilli. Rifampicin is the most potent sterilizing drug available. Pyrazinamide and streptomycin are also bactericidal against certain populations of TB bacilli. Pyrazinamide is active only in an acid environment. Streptomycin is bactericidal against rapidly multiplying TB bacilli. Ethambutol and thioacetazone are used in association with more powerful drugs to prevent the emergence of resistant bacilli.

Table 4.1 shows the essential antituberculosis drugs and their recommended dosage (range in parentheses).

Table 4.1 Essential antituberculosis drugs

ESSENTIAL DRUG (ABBREVIATION)	RECOMMENDED DOSAGE (DOSE RANGE), mg/kg	
	DAILY	3 TIMES WEEKLY ^a
isoniazid (H)	5 (4–6)	10 (8–12)
rifampicin (R)	10 (8–12)	10 (8–12)
pyrazinamide (Z)	25 (20–30)	35 (30–40)
streptomycin (S)	15 (12–18)	15 (12–18)
ethambutol (E)	15 (15–20)	30 (20–35)
thioacetazone ^b (T)	2.5	Not applicable

^a WHO does not recommend twice-weekly regimens. If a patient receiving a twice-weekly regimen misses a dose of tablets, this missed dose represents a larger fraction of the total number of treatment doses than if the patient were receiving a thrice-weekly or daily regimen. There is therefore an increased risk of treatment failure. Moreover, HIV-positive patients receiving therapy with twice-weekly doses or less are at increased risk of failure or relapse with acquired rifampicin-resistant TB.

^b WHO discourages the use of thioacetazone because of the risk of severe toxicity, in particular in HIV-infected individuals. It should be replaced by ethambutol, especially in areas where HIV infection is common. Thioacetazone may be used in combination with isoniazid in the continuation phase in areas with low prevalence of HIV infection when financial circumstances preclude the use of ethambutol.

Annex 2 provides information on the recommended dosage and common adverse events of essential antituberculosis drugs. The WHO-recommended formulations of antituberculosis drugs and fixed-dose combinations (FDCs) of drugs appear in the WHO Model List of Essential Drugs (1). The available formulations and combinations of antituberculosis drugs within each country should conform to this List.

Fixed-dose combination tablets

Tablets of fixed-dose drug combinations have several advantages over individual drugs. First, prescription errors are likely to be less frequent because dosage recommendations are more straightforward and adjustment of dosage according to patient weight is easier. Second, the number of tablets to ingest is smaller and may thus encourage patient adherence. Third, if treatment is not observed, patients cannot be selective in the choice of drugs to ingest.

Fixed-dose combinations of drugs also have disadvantages. First, if prescription errors do occur, excess dosage (risk of toxicity) or sub-inhibitory concentrations of all drugs (favouring development of drug resistance) may result. Second,

health care workers may be tempted to evade directly observed therapy, erroneously believing that adherence is automatically guaranteed. Third, poor rifampicin bioavailability has been found for some FDCs, particularly in 3- and 4-drug combinations. Quality assurance is therefore essential. Finally, using FDCs does not obviate the need for separate drugs for a minority of patients who develop drug toxicity.

WHO strongly recommends the use of FDC tablets for the treatment of TB. The recommended formulations currently available are shown in Table 4.2.

Table 4.2 WHO-recommended formulations of essential antituberculosis drugs^a

DRUG	DOSE FORM	STRENGTH
Separate drugs		
isoniazid	tablet	100 mg, 300 mg
rifampicin	tablet or capsule	150 mg, 300 mg
pyrazinamide	tablet	400 mg
ethambutol	tablet	100 mg, 400 mg
streptomycin	powder for injection in vial	1 g

DRUG	DOSE FORM	STRENGTH FOR DAILY USE	STRENGTH FOR USE 3 TIMES WEEKLY
Fixed-dose combinations of drugs			
isoniazid + rifampicin	tablet	75 mg +150 mg 150 mg +300 mg	150 mg + 150 mg
	tablet or pack of granules ^b	30 mg + 60 mg	60 mg + 60 mg
isoniazid + ethambutol	tablet	150 mg + 400 mg	-
isoniazid + thioacetazone	tablet	100 mg + 50 mg	-
		300 mg + 150 mg	-
isoniazid + rifampicin + pyrazinamide	tablet	75 mg + 150 mg + 400 mg	150 mg + 150 mg + 500mg
	tablet or pack of granules ^b	30 mg+60 mg+150 mg	
isoniazid + rifampicin + pyrazinamide + ethambutol	tablet	75 mg + 150 mg + 400 mg + 275 mg	-

^a From Essential drugs: WHO Model List (revised December 1999). In: *WHO Drug Information*, 1999, 13(4): 249–262.

^b For paediatric use.

Intermittent use

Isoniazid, rifampicin, pyrazinamide and streptomycin are all as efficacious when given three times weekly as when given daily. Thioacetazone is the only antituberculosis drug that is ineffective when given intermittently.

Thrice-weekly drug intake facilitates observation, reduces costs and inconvenience for the patient because of fewer visits, and liberates staff for patient retrieval on alternate days. Fully intermittent regimens are used in the two largest TB programmes (China and India), with high levels of effectiveness under programme conditions.

Standardized regimens

The choice by each country of a limited number of standardized regimens should be based on the availability of financial resources, efficacy, effectiveness and applicability in the current health system network, and population distribution and mobility. Standardized regimens have the following advantages over individualized prescription of drugs:

- reduce errors in prescription thereby reducing the risk of development of drug resistance
- facilitate estimates of drug needs, purchasing, distribution and monitoring
- facilitate staff training
- reduce costs
- facilitate regular drug supply when patients move from one area to another.

To facilitate procurement, distribution and administration of treatment to patients, daily dosage may be standardized for three or four body weight bands - for instance, 30-39, 40-54, 55-70 and >70 kg (see Annex 4) - or a single dosage given for most patients, with additional rifampicin for patients >60 kg and individual calculation for children, as in India.

4.4 Recommended standardized treatment regimens

New cases

Treatment regimens have an initial (or intensive) phase lasting 2 months and a continuation phase usually lasting 4 or 6 months. During the initial phase, normally consisting of isoniazid, rifampicin, pyrazinamide and ethambutol, the tubercle bacilli are killed rapidly. Infectious patients quickly become non-infectious (within approximately two weeks). Symptoms abate. Most patients with sputum smear-positive TB become smear-negative within two months. During the continuation phase, fewer drugs are necessary but they must be given for a longer time. The sterilizing effect of the drugs eliminates the remaining bacilli and prevents subsequent relapse.

Patients with a large bacillary load (smear-positive PTB and many HIV-infected patients with smear-negative PTB) have an increased risk of selecting resistant bacilli because a large population of bacilli develops spontaneous resistance to a single drug. Short-course chemotherapy regimens, consisting of 4 drugs during the initial phase and 2 drugs during the continuation phase, reduce this risk. Such regimens are highly effective in patients with susceptible bacilli, and almost as effective in patients with initially isoniazid-resistant organisms.

Patients negative for HIV, with smear-negative pulmonary or extrapulmonary TB that is fully drug-susceptible, have little risk of selecting resistant bacilli because their lesions generally harbour fewer bacilli. However, since initial resistance to isoniazid is common in many areas, and HIV testing of tuberculosis patients is not routinely practised, it is now recommended that ethambutol be included as a fourth drug during the initial phase of treatment for most patients with smear-negative PTB and EPTB. Ethambutol may be omitted for patients with non-cavitary, smear-negative pulmonary TB who are known to be HIV-negative, patients known to be infected with fully drug-susceptible bacilli, and young children with primary TB.

Re-treatment cases

Previously treated TB patients include those patients treated as new cases for more than one month who are now smear- or culture-positive (failure, relapse, return after default). Re-treatment cases have a higher likelihood of drug resistance, which may have been acquired through inadequate prior chemotherapy. They are also more likely than new patients to harbour and excrete bacilli resistant to at least isoniazid. The re-treatment regimen consists of 5 drugs in the initial phase and 3 drugs in the continuation phase. Three of the drugs - RHE - are given throughout the treatment. This standardized regimen can cure patients excreting bacilli still fully sensitive to the drugs and those excreting bacilli resistant to isoniazid and/or streptomycin. Under proper case management conditions, MDR-TB cases are those most at risk of failure in the re-treatment regimen.

4.5 Rationale for prioritizing TB diagnostic categories

From a public health perspective, the highest priority of an NTP is the identification and cure of infectious TB cases, i.e. patients with sputum smear-positive PTB. In settings of resource constraint, the rational allocation of resources is necessary to prioritize diagnostic categories according to the impact and cost-effectiveness of treatment for each category. Diagnostic categories are therefore ranked from I (highest priority) to IV (lowest priority).

The new WHO recommendations for TB treatment regimens appropriate to the different diagnostic categories (shown in Table 4.3) reflect developments in drug formulations and advances in understanding the response to TB treatment in HIV-infected persons. For example, the benefits of using a single regimen with 4 drugs in the initial phase of treatment for all new patients may outweigh the

disadvantages (including over-treatment of many patients with non-severe smear-negative PTB and EPTB).

4.6 Standard code for TB treatment regimens

Treatment regimens for TB have a standard code. Each antituberculosis drug has an abbreviation (shown in Table 4.1).

A TB treatment regimen consists of two phases: an initial phase and a continuation phase. The number before a phase is the duration of that phase in months. Letters in parentheses indicate fixed-dose combinations of those drugs. A subscript number (e.g. 3) after a letter or letters in parentheses indicates the number of doses of that drug per week. If there is no subscript number, treatment is daily (or 6 times weekly, excluding, for instance, Sundays). Examples are shown below. An alternative drug (or drugs) appears as a letter (or letters) in square brackets.

Examples

2 (HRZE)/4 (HR)₃

The initial phase is 2 (HRZE). The duration of the phase is 2 months. Drug treatment is daily, with isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E) in fixed-dose combination.

The continuation phase is 4 (HR)₃. The duration is 4 months, with isoniazid and rifampicin, in fixed-dose combination, 3 times per week.

2 (HR)ZE/6 (HE)

The initial phase is 2 (HR)ZE. The duration of the phase is 2 months. Drug treatment is daily, with isoniazid (H) and rifampicin (R) in fixed-dose combination, plus pyrazinamide (Z) and ethambutol (E).

The continuation phase is 6 (HE). The duration of the phase is 6 months. Drug treatment is daily, with isoniazid (H) and ethambutol (E) in fixed-dose combination.

4.7 Recommended treatment regimens for TB diagnostic categories

There are several possible regimens. The regimens recommended in each country's NTP depend on that country's budget, access of patients to PHC services, qualifications of health staff at peripheral level and current best medical practice. The regimen recommended for each patient depends on the diagnostic category for each patient. Table 4.3 and section 4.8 show alternative regimens for each diagnostic category, which can be used in various circumstances and in certain sub-populations. National TB programmes should decide the most appropriate regimens to be followed at national level.

Table 4.2 shows the recommended formulations of essential antituberculosis drugs.

Tables 1 to 4 in Annex 4 show the number of tablets by body weight band appropriate for most TB patients.

Table 4.3 Recommended treatment regimens for each diagnostic category

TB DIAGNOSTIC CATEGORY	TB PATIENTS	TB TREATMENT REGIMENS	
		INITIAL PHASE (DAILY OR 3 TIMES WEEKLY) ^a	CONTINUATION PHASE (DAILY OR 3 TIMES WEEKLY) ^a
I	New smear-positive patients; New smear-negative PTB with extensive parenchymal involvement; Severe concomitant HIV disease or severe forms of EPTB	2 HRZE ^b	4 HR or 6 HE daily ^c
II	Previously treated sputum smear-positive PTB: - relapse; - treatment after interruption; - treatment failure ^d	2 HRZES/1 HRZE	5 HRE
III	New smear-negative PTB (other than in Category I); Less severe forms of EPTB	2 HRZE ^e	4 HR or 6 HE daily ^c
IV	Chronic and MDR-TB cases (still sputum-positive after supervised re-treatment) ^f	Specially designed standardized or individualized regimens are suggested for this category See Chapter 5	

^a Direct observation of drug intake is required during the initial phase of treatment in smear-positive cases, and always in treatment that includes rifampicin.

^b Streptomycin may be used instead of ethambutol. In meningeal TB, ethambutol should be replaced by streptomycin.

^c This regimen may be associated with a higher rate of treatment failure and relapse compared with the 6-month regimen with rifampicin in the continuation phase (see section 4.8)

^d Whenever possible, drug sensitivity testing is recommended before prescribing Category II treatment in failure cases. It is recommended that patients with proven MDR-TB use Category IV regimens (see Chapter 5).

^e Ethambutol may be omitted during the initial phase of treatment for patients with non-cavitary, smear-negative PTB who are known to be HIV-negative, patients known to be infected with fully drug-susceptible bacilli, and young children with primary TB.

^f Contacts of patients with culture-proven MDR-TB should be considered for early culture and sensitivity testing.

4.8 Considerations for the choice of continuation phase regimen in new patients (Category I and III)

National TB programmes may choose one of the continuation phase regimens listed in Table 4.3. Some advantages and disadvantages are noted below. However, national recommendations should be as simple as possible, and avoid multiple alternatives, to facilitate training, drug procurement and supply, and drug administration, and to avoid errors in prescription. The options are:

- **4 HR** daily or 3 times weekly as directly observed treatment. The effectiveness is the same. In daily directly observed treatment, the patient must attend the health facility or meet the treatment observer more frequently, with increased cost and loss of time. Treatment 3 times weekly allows the treatment observer to dedicate alternate days to find and recover patients who interrupted treatment. However, daily treatment may be more appropriate if the patient is hospitalized, or if the observer is nearby (neighbour) or at the patient's home (for example mother to small child). **Use of FDCs is highly recommended.**
- **6 (HE)¹** daily, self-administered treatment, with drug supply every two weeks to one month. There is no assurance that the patient is taking all the drugs, and treatment interruption is noted only when the patient does not return to collect drugs. Moreover, preliminary results from an international multicentre randomized clinical trial suggest that the combined rate of treatment failure and relapse for this regimen is higher than that for the 6-month regimen with rifampicin throughout (12% versus 3%). However, the advantage is that mobile populations and patients with very limited access to health services need direct observation only in the initial phase (either through hospitalization or by moving closer to health facilities for a limited time). It is particularly appropriate for countries with limited PHC access and unable to organize a system of direct observation through health facilities, community health workers or volunteers. In addition, not using rifampicin in the continuation phase may reduce acquired resistance to this drug. While less effective than HR, the HE regimen is expected to cure the large majority of adherent patients, and its use allows reliance on a rifampicin-based re-treatment regimen for patients who fail or relapse. Unlike the 4 HR continuation phase, this regimen can also be used concomitantly with antiretrovirals among HIV-infected patients. **Only FDCs should be used.**

4.9 Considerations for the choice of regimen for cases who fail Category I regimen

The first alternative for NTPs with limited resources is to use a Category II regimen, as for other re-treatment cases. However, failures to regimen I have a

¹ Some countries still use HT (isoniazid/thioacetazone) instead of HE. WHO discourages the use of thioacetazone because of the risk of toxicity; however, it may be continued in countries where HIV infection is uncommon and financial considerations preclude the general use of HE.

higher probability of being multidrug-resistant, particularly if the whole treatment was directly observed and included rifampicin in the continuation phase. Regimen II has poor results in MDR-TB cases (less than 50% cure rate). An option for countries implementing regimen IV with reserve drugs is to use this regimen in failures to regimen I with proven MDR-TB. This requires sufficient resources (clinical, laboratory and drugs), availability of culture and reliable susceptibility testing, and capacity to maintain patients on treatment for long periods (see Chapter 5). Before regimen IV is used routinely for those who fail Category I regimen, the NTP should first strengthen the management of Category I patients, including putting all patients on directly observed therapy. Only after further strengthening case management practices should the programme move to provide reserve antituberculosis drugs.

Failures to Category I treatment regimen may not always have MDR-TB, particularly if the entire treatment was not directly observed or if the continuation phase did not include rifampicin. National TB programmes may therefore provide the standard Category II re-treatment regimen until the results of susceptibility testing (if available) are known. This will enable a more efficient use of available resources. **Culture and susceptibility testing should be performed as soon as patients fail treatment.** A reference laboratory that is quality controlled should perform susceptibility testing. This will often require use of an external laboratory in order to obtain accurate and reliable results.

4.10 Treatment of extrapulmonary TB

Although most commonly affecting the lungs, TB can involve virtually any organ of the body. In countries with comprehensive diagnostic and reporting systems, EPTB accounts for 20-25% of reported cases, being relatively more frequent in children and persons with HIV infection. Of specific forms, lymphatic, pleural, and bone or joint disease are the most common, while pericardial, meningeal, and disseminated (miliary) forms are more likely to result in a fatal outcome.

In general, EPTB is more difficult to diagnose than pulmonary disease, often requiring invasive procedures to obtain diagnostic specimens and more sophisticated laboratory techniques than sputum microscopy. From a public health perspective, EPTB is not of great importance, because patients with this form of disease are not infectious unless they also have pulmonary involvement. Perhaps as a consequence of these two factors, most guidelines for TB treatment intended for use in low-income countries have not addressed in any detail the treatment of EPTB.

Treatment recommendations are further complicated by the paucity of data from controlled clinical trials of extrapulmonary forms of TB. In the pre-rifampicin era, most experts believed that 18-24 months of isoniazid-based treatment (together with *p*-aminosalicylic acid or ethambutol and supplemented by initial streptomycin) was required to achieve satisfactory results. Subsequently, a number of clinical trials demonstrated that rifampicin-based treatment for 6-9 months gave comparable results. Consequently, most experts now agree that virtually all forms of EPTB can be treated with the regimens shown in Table 4.3.

Eight-month regimens (2 HRZ/6 HE) have not been evaluated in EPTB, but would probably be satisfactory for treatment of less severe forms of disease. In meningeal TB, a 6-month regimen with rifampicin throughout was shown to be as effective as the traditional 9-12 month-regimens, with streptomycin used instead of ethambutol in the initial phase¹. Finally, adjunctive steroids may be useful in pericardial and meningeal TB. Surgery plays little role in the treatment of EPTB, being reserved for management of late complications of disease such as hydrocephalus, obstructive uropathy, constrictive pericarditis, and neurological involvement from Pott disease (spinal TB).

4.11 Treatment regimens in special situations

Pregnancy

A woman should be asked whether she is pregnant before she starts TB treatment. Most antituberculosis drugs are safe for use in pregnancy. The exception is streptomycin, which is ototoxic to the fetus and should not be used during pregnancy. A pregnant woman should be advised that successful treatment of TB with the recommended standardized regimen is important for successful outcome of pregnancy.

Breastfeeding

A breastfeeding woman who has TB should receive a full course of TB treatment. Timely and properly applied chemotherapy is the best way to prevent transmission of tubercle bacilli to her baby. All antituberculosis drugs are compatible with breastfeeding; a woman taking them can safely continue to breastfeed. Mother and baby should stay together and the baby continue to be breastfed in the normal way. The baby should be given prophylactic isoniazid for at least 3 months beyond the time the mother is considered to be non-infectious. BCG vaccination of the newborn should be postponed until the end of isoniazid prophylaxis.

Oral contraception

Rifampicin interacts with oral contraceptive medications with a risk of decreased protective efficacy against pregnancy. A woman receiving oral contraception may choose between two options while receiving treatment with rifampicin: following consultation with a clinician, an oral contraceptive pill containing a higher dose of estrogen (50 µg) may be taken, or another form of contraception may be used.

Liver disorders

Isoniazid, rifampicin and pyrazinamide are all associated with hepatitis. Of the three drugs, rifampicin is least likely to cause hepatocellular damage, although it

¹ See Phuapradit P, Vejjajiva A. Treatment of tuberculosis meningitis: role of short-course chemotherapy. *Quarterly Journal of Medicine*, 1987, 62(239):249-258; Anane T. Analyse des résultats de la chimiothérapie courte de six mois dans la tuberculose de l'enfant en Algérie. In: Pons G, Gendrel D, Grosset J, eds. *Les médicaments de la tuberculose chez l'enfant*. Paris, Springer Verlag, 1999; van Loenhout-Rooyackers et al. Tuberculosis meningitis: is a 6-month treatment regimen sufficient? *International Journal of Tuberculosis and Lung Disease*, 2001, 5(11):1028-1035.

is associated with cholestatic jaundice. Of the three agents, pyrazinamide is the most hepatotoxic.

Patients with the following conditions can receive the usual short-course chemotherapy regimens provided there is no clinical evidence of chronic liver disease - hepatitis virus carriage, a past history of acute hepatitis, excessive alcohol consumption. However, hepatotoxic reactions to antituberculosis drugs may be more common among these patients and should therefore be anticipated.

Established chronic liver disease

Patients with liver disease should not receive pyrazinamide. Isoniazid plus rifampicin plus one or two non-hepatotoxic drugs such as streptomycin and ethambutol can be used for a total treatment duration of 8 months. Alternative regimens are 9 RE or SHE in the initial phase followed by HE in the continuation phase, with a total treatment duration of 12 months. Recommended regimens are therefore 2 SHRE/6 HR, 9 RE or 2 SHE/10 HE.

Acute hepatitis (e.g. acute viral hepatitis)

Uncommonly, a patient has TB and concurrently acute hepatitis unrelated to TB or TB treatment. Clinical judgement is necessary. In some cases, it is possible to defer TB treatment until the acute hepatitis has resolved. In other cases, when it is necessary to treat TB during acute hepatitis, the combination of SE for 3 months is the safest option. If the hepatitis has resolved, the patient can then receive a continuation phase of 6 months isoniazid and rifampicin 6 HR. If the hepatitis has not resolved, SE should be continued for a total of 12 months.

Renal failure

Isoniazid, rifampicin and pyrazinamide are either eliminated almost entirely by biliary excretion or metabolized into non-toxic compounds. These drugs can therefore be given in normal dosage to patients with renal failure. Patients with severe renal failure should receive pyridoxine with isoniazid in order to prevent peripheral neuropathy.

Streptomycin and ethambutol are excreted by the kidney. Where facilities are available to monitor renal function closely, streptomycin and ethambutol may be given in reduced doses. Thioacetazone is partially excreted in the urine; however, since the margin between a therapeutic dose and a toxic dose is too narrow, patients in renal failure should not receive this drug. The safest regimen for patients with renal failure is 2 HRZ/4 HR.

HIV infection

Generally, TB treatment is the same for HIV-infected as for non-HIV-infected TB patients, with the exception that thioacetazone is contraindicated in those who are HIV-infected. Streptomycin remains a useful drug in countries able to ensure the use of sterile needles and syringes. Deaths during treatment, partly due to TB itself and partly due to other HIV-related diseases, are more frequent in HIV-

infected patients, particularly in the advanced stages of immunodeficiency. If a pregnant woman is known to be HIV-positive, the availability of antiviral treatment to prevent mother-to-child transmission should be considered. Chapter 10 provides more detailed information.

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MANAGEMENT OF CHRONIC AND MULTIDRUG-RESISTANT CASES

5.1 Objectives of chapter

This chapter describes the different treatment options with reserve¹ antituberculosis drugs for chronic and MDR-TB cases previously treated under proper management conditions with the essential antituberculosis drugs. This assumes that the necessary resources for procuring these drugs and ensuring their proper use are available.

5.2 Definitions

Chronic. A patient with TB who is sputum-positive at the end of a standard re-treatment regimen with essential antituberculosis drugs.

MDR-TB. A patient who has active tuberculosis with bacilli resistant at least to both rifampicin and isoniazid.

5.3 Background

Chronic cases and MDR-TB cases are not synonymous. MDR-TB can rarely be observed in new cases; it is more frequent in re-treatment cases, especially in failure cases. MDR-TB is one of the main causes of failure to a Category I treatment regimen in patients who are treated under strict observation. Studies conducted in Peru and Viet Nam, two countries in which DOTS has been implemented successfully, have shown that Category I treatment failures commonly have MDR-TB.

Chronic patients probably have MDR-TB because they have previously received at least two full courses of treatment with essential antituberculosis drugs. The aims of treatment of chronic and MDR-TB cases are similar to those of all cases with TB (see Chapter 4). However, MDR-TB patients respond poorly to short-course chemotherapy and need to be treated intensively and for up to 24 months with a regimen based on reserve antituberculosis drugs.

Multidrug-resistant TB is a major cause of failure for the individual patients concerned. Management of chronic cases becomes an objective for an NTP when the DOTS strategy is fully implemented. Full implementation of DOTS is the best prevention against chronic disease and extension of MDR-TB. In programmes that have applied the strategy for several years (Algeria, Côte d'Ivoire, Morocco, Peru, South Africa, United Republic of Tanzania), chronic cases represent less than 2% of the total smear-positive PTB cases. Careful cohort analysis of these subgroups of re-treatment cases is essential to assess the magnitude of chronic cases and, whenever possible, the proportion of MDR-TB among chronic cases.

¹ The term "reserve" is used instead of "second-line", in accordance with the WHO Model List of Essential Drugs.

5.4 Managerial principles

The main priority for TB control is the identification and cure of sputum smear-positive pulmonary TB cases. The decision to use regimens incorporating reserve antituberculosis drugs should thus be based on:

- the availability of additional financial resources for reserve drugs;
- the capacity of the NTP to maintain patients on regular treatment;
- laboratories that can perform high-quality drug susceptibility testing;
- prevention of uncontrolled use of reserve drugs;
- special registration of chronic and MDR-TB cases and expert committee(s) for decisions on treatment and monitoring;
- special cohort analysis.

Without an effective organizational framework, such as the one suggested in the DOTS strategy, and without knowledge of the operational requirements of treatment with reserve regimens, the chances of success will be minimal.

Treatment of chronic and MDR-TB cases with reserve drugs is more expensive and more toxic than treatment with essential drugs. Many programmes will therefore choose hospitalization, at least for the initial portion of therapy. However, hospitalization entails increased risk of nosocomial transmission of MDR-TB to both staff and patients, especially those infected with HIV. After tolerance of the drug regimen has been ascertained and the patient's cooperation has been secured, the patient can be started on ambulatory treatment. Programmes with strong home-based care, well-trained visiting health care workers and/or capable health care centres may choose to have ambulatory treatment from the outset. Ambulatory treatment reduces the risk of MDR-TB transmission in hospitals, which often lack adequate infection control capacity.

Management of chronic and MDR-TB cases with reserve drugs can be done in different ways. If standardized regimens are used, feasibility of their administration under the aegis of the NTP is conditional on a strong NTP that is successfully applying the DOTS strategy. Advantages of standard regimens include potential reduction of costs compared with individualized regimens, reduction of errors in prescription, easier estimation of drug needs, purchasing, distribution, and monitoring, facilitation of staff training, and facilitation of regular drug supply when patients move from one area to another.

Centres of excellence, to which patients are referred for treatment, could utilize individualized regimens tailored to the drug susceptibility pattern of the patient. Referral to such facilities may also be the best option for patients whose cooperation is not easy to achieve, such as individuals suffering from alcoholism or drug dependence, prisoners, and homeless persons. Special efforts are needed to persuade such patients to complete the long and arduous treatment regimens

required. The advantages of individualized regimens include treatment according to the susceptibility pattern and, probably, higher cure rates. This approach may, however, be more costly than standardized regimens in terms of the drugs involved, in laboratory capability and in the training required to administer a variety of treatment regimens.

Use of standardized or individualized treatment regimens is currently the subject of operational studies to assess the feasibility and cost-effectiveness of using reserve drugs under the aegis of the NTP in resource-limited countries. Evidence from Peru shows that use of standardized regimens at country level may be feasible and cost-effective (1).

5.5 Principles of treatment

The treatment regimen should include at least 4 drugs, including an injectable agent and a fluoroquinolone in the initial phase, and at least 3 of the most active and best-tolerated drugs in the continuation phase. An initial phase of at least 6 months should be followed by a continuation phase of 12-18 months.

While drug susceptibility testing may not be available in some resource-limited settings, all efforts should be made to obtain an accurate essential drug susceptibility testing profile of patients failing short-course chemotherapy and of chronic disease in order to confirm the presence of MDR. Programmes planning to implement the use of reserve drugs in a standardized regimen but unable to perform susceptibility testing should set up relationships with supranational laboratories until such facilities can be established locally.

Standardized regimens are the choice in settings where susceptibility testing of reserve drugs is not available. However, drug susceptibility testing is recommended in patients who fail the standardized regimen and, when possible, these cases should be referred to specialized centres for individualized treatment.

Use of regimens tailored to the susceptibility pattern of reserve drugs requires highly specialized laboratory and microbiological follow-up - facilities that are not yet available in most resource-limited countries.

5.6 Logistic issues

The management of chronic and MDR-TB cases requires operational organization that allows integration within the NTP. An expert committee of TB specialists, public health specialists and laboratory specialists should be appointed to screen requests from general health facilities for access to treatment with reserve drugs. The committee could be national, or several regional committees can be constituted. This is very important, since central level NTP staff do not usually have time to look into these issues - their most important priority is the management of new cases to prevent the development of chronic and MDR-TB.

A register of the chronic cases and MDR-TB identified should be created, for follow-up and treatment outcome at the end of treatment.

Some countries have created a special unit under the aegis of the NTP to coordinate meetings of the special committee, for data management and analysis, to solve problems, to oversee delivery of reserve drugs and for other operational activities. This unit is an appendage of the NTP. The minimum personnel requirements are a project coordinator (who responds to the NTP manager), a nurse, a medical coordinator and a data manager.

Coordination with the laboratory is vital. Usually only one reference laboratory capable of susceptibility testing of essential drugs (to confirm MDR) is available. It is therefore important that the reference laboratory works in close coordination with the special unit.

5.7 Reserve antituberculosis drugs

Reserve drugs are a last resort for the management of chronic or MDR-TB cases. Table 5.1 shows the reserve antituberculosis drugs, their mode of action and recommended dosage. The market status and price of reserve drugs in 2001 can be found in Gupta et al (2). Annex 3 provides information on the common side-effects of these drugs.

Table 5.1 Reserve antituberculosis drugs

RESERVE DRUG (ABBREVIATION)	MODE OF ACTION	RECOMMENDED DAILY DOSAGE ^a		
		AVERAGE (mg/kg)	MINIMUM (mg)	MAXIMUM (mg)
amikacin (Am)	bactericidal	15	750	1000
capreomycin (Cm)	bactericidal	15	750	1000
ciprofloxacin (Cx)	bactericidal	10–20	1000	1500
cycloserine (Cs)	bacteriostatic	10–20	500	750
ethionamide (Et)	bactericidal	10–20	500	750
kanamycin (Km)	bactericidal	15	750	1000
ofloxacin (O)	bactericidal	7.5–15	600	800
<i>p</i> -aminosalicylic acid (PAS)	bacteriostatic	150	8 g	12 g
protionamide (Pt)	bactericidal	10–20	500	750

^a Thrice-weekly regimens are not recommended.

5.8 Designing a treatment regimen

A standardized re-treatment regimen should include at least 4 drugs never used by the patient, including an injectable (capreomycin, amikacin or kanamycin) and a fluoroquinolone (see Table 5.2). Treatment should be given daily and directly observed. Bacteriological results (smear and, if possible, culture) should be monitored. Pyrazinamide and ethambutol can be included in the regimen because of the lower probability of resistance than to other essential drugs. However, in chronic cases that have received multiple treatments, using ethambutol and pyrazinamide, it is doubtful whether these drugs remain active, and including them may offer little advantage. An initial phase of at least 6 months should be followed by a continuation phase of 12-18 months with at least 3 of the most active and best-tolerated drugs.

If the results of susceptibility tests for essential and reserve drugs are available and the full range of reserve drugs is available, the treatment regimen may be tailored according to the susceptibility pattern. Designing a regimen will depend on several factors, such as the drugs to which the strain of *M. tuberculosis* is resistant. The same principles - at least 4 drugs never used, including an injectable and a fluoroquinolone, and an initial phase of at least 6 months followed by a continuation phase of 12-18 months - apply.

Treatment regimens with reserve antituberculosis drugs remain much more expensive than regimens with essential antituberculosis drugs. In countries with limited financial resources, health facilities and staff, the provision of regimens with reserve drugs may be an unacceptable drain on resources. **It would be irrational for any country to divert resources to regimens with reserve drugs if a large proportion of new infectious cases remain untreated or ineffectively treated and short-course chemotherapy with drugs has not reached its full therapeutic potential.** A large requirement for reserve drugs reflects poor-quality implementation of short-course treatment.

Furthermore, since there is poor tolerance to some of the reserve drugs and their efficacy is limited, the best strategy is to prevent chronic cases (and MDR-TB) through full implementation of the DOTS strategy and standardized short-course regimens Category I and II.

Access to specially priced, quality-assured reserve drugs can be possible through the Green Light Committee (GLC). In addition, the GLC offers technical assistance and a regular monitoring mechanism for projects. Programmes considering the use of reserve drugs should strongly consider using the GLC mechanism to help ensure that all parameters are in place to guarantee successful treatment outcomes.

Table 5.2 Suggested treatment regimens

SUSCEPTIBILITY TESTING TO ESSENTIAL DRUGS	INITIAL PHASE		CONTINUATION PHASE	
	DRUGS	DURATION	DRUGS	DURATION
Not available^a	Km ^b + Et + Q ^c + Z +/- E	At least 6 months	Et + Q + Z +/- E	12–18 months
Available:				
Resistance to H + R	S ^d + Et + Q ^c + Z +/- E	At least 6 months	Et + Q + Z +/- E	12–18 months
Resistance to all essential drugs	1 injectable + 1 fluoroquinolone + 2 of these 3 oral drugs: PAS, Et, Cs	At least 6 months	The same drugs except injectable	18 months
Susceptibility testing to reserve drugs available	Tailor regimen according to susceptibility pattern ^e			

^a Use of a standardized regimen could be feasible in resource-limited countries with a high burden of TB and a strong and efficient NTP.

^b Am or Cm could also be used. However, since there is cross-resistance between Km and Am, if either drug was used previously or if resistance to them is suspected, Cm is the preferred choice.

^c Fluoroquinolone (ciprofloxacin or ofloxacin).

^d If resistance to S is confirmed, replace this drug with Km, Am or Cm.

^e Individualized regimen is probably more feasible in designated centres of excellence.

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Suggestions for further reading

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Instructions for applying to the Green Light Committee for access to second-line anti-tuberculosis drugs. Geneva, World Health Organization, 2002 (document WHO/CDS/TB/2001.286 Rev 1).

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6

ADHERENCE TO TREATMENT**6.1 Objectives of chapter**

The public health priority of an NTP is the cure of smear-positive TB cases, while preventing the emergence of drug resistance. Adherence to treatment should be ensured to achieve this priority. This chapter provides recommendations on how to ensure treatment compliance.

Because of the importance of tuberculosis in public health, drugs for TB treatment should be provided free of charge to all patients.

6.2 Ensuring patient compliance versus defaulter tracing

Patient compliance is a key factor in treatment success. In many countries, a significant proportion of patients stop treatment before completion, for various reasons. The premature interruption of treatment represents a problem for patients, their families and those who care for them, and those responsible for TB programmes.

Promoting compliance through a patient-centred approach, which includes facilitating access to treatment, choosing with the patient the most convenient time and place for direct observation of treatment and, when possible, providing other social and medical services, is much more effective than spending resources on defaulter tracing. Facilitating access includes providing drugs and sputum smear controls free of charge, reducing the time and cost to the patient of obtaining treatment, and providing good and rapid attention.

Convenience to the patient must be balanced against the assurance of regular drug intake and monitoring, important to give the patient the best chances of cure. Patients who self-administer treatment often take drugs irregularly, and tracing is difficult and often unproductive, especially in low-income countries. In addition, there is a much longer period between interruption of treatment and action by the health system.

It is vital for health staff and community workers to offer polite and efficient attention, and to consider the needs of the patient at every contact with them.

6.3 Directly observed treatment: questions and answers**6.3.1 What is directly observed treatment?**

Directly observed treatment (DOT) is an important element in the internationally recommended policy package for TB control. Directly observed treatment means that an observer watches the patient swallowing their tablets, in a way that is sensitive and supportive to the patient's needs. This ensures that a TB patient

takes the right antituberculosis drugs, in the right doses, at the right intervals. Many countries have used DOT in inpatient settings in hospitals or in sanatoria. Directly observed treatment is also applicable in outpatient settings. In practice, it means providing a treatment observer acceptable to the patient, to enable the patient to complete treatment. The observer may be a health worker or a trained and supervised community member. There may be an incentive of some sort for community members to become observers of TB treatment. The NTP is responsible for training and monitoring the community treatment observers. There must be a clearly defined line of accountability from NTP staff to general health services staff and the treatment observer. It is important to ensure confidentiality and the acceptability of directly observed treatment to the patient. The drugs should remain with the treatment observer and be given to the patient only at the time of intake.

6.3.2 *Why directly observed treatment?*

Directly observed treatment is required to ensure treatment adherence. It helps to reinforce patients' motivation to continue treatment and counters the tendency of some to interrupt treatment – it is impossible to predict who will or will not comply. Directly observed treatment also ensures the accountability of TB services and helps to prevent the emergence of drug resistance. It is recommended in:

- the initial phase of treatment, at least for all smear-positive cases;
- the continuation phase of rifampicin-containing (daily and thrice weekly) regimens.

A patient who misses one attendance for DOT should be traced and returned to treatment.

When DOT for all patients throughout the whole treatment is not always practicable, it is recommended to use the 8-month regimen containing isoniazid plus ethambutol for daily self-administration in the continuation phase, with monthly clinical visits and medication refills.

6.3.3 *How should directly observed treatment be applied to fit patients' needs?*

A TB patient who has far to travel for treatment is less likely to adhere to treatment. One of the aims of a TB programme is to organize TB services so that the patient has treatment as close to home (or the workplace) as possible. An NTP brings services close to patients by integrating TB services with general health services.

Many TB patients live close to a health facility (e.g. health centre, health post, hospital). For them, the treatment observer will be one of the staff in the health facility, and this should be the chosen alternative if it fits the patient's convenience. Some TB patients live far away from a health facility. For them, the treatment observer will be a community health worker or a trained local

community member. In general, members of the patient's family should not serve as treatment observers. Collaboration with other programmes allows the identification of staff from these programmes (e.g. leprosy control), who may observe TB treatment. Some areas have HIV/AIDS community care schemes. The HIV/AIDS home care providers with suitable training and monitoring can observe TB treatment.

6.3.4 *How should directly observed treatment be facilitated?*

The aim is to maximize ambulatory treatment as close to the patient's home (or workplace) as possible. Where possible, general health service staff should directly observe treatment. When this is not possible, community members can directly observe treatment. Cured patients may also be successful DOT providers.

Where possible, use fixed-dose combinations (see Chapter 4 and Annex 2) and blister packs to help reduce medication error.

Incentives for volunteers and patients may be considered, bearing in mind the advantages and disadvantages of incentive schemes.

6.3.5 *Community support of TB patients, including directly observed treatment*

National TB programmes, health services and communities should seriously consider how they can promote community contribution to TB care in their respective settings. This is especially so for settings where the TB case-load is overwhelming available resources. Community-based DOT may be used to expand access to treatment for some underserved patient groups and to further improve treatment outcomes. Community contribution to TB care should be seen as complementing and extending NTP capacity, not replacing NTP activity.

Recommendations

- Effective community contribution to TB care, especially community-based DOT, requires a strong reporting system, access to laboratory facilities and a secure drug supply, through the NTP.
- Existing community groups and organizations should first be approached to determine how they may be able to make a contribution to community TB care, rather than setting up new systems, groups and organizations.
- While community care and DOT are cheaper and more cost-effective than hospital-based care, resources are needed for training and supervising community treatment observers. Community volunteers need regular support, motivation, instruction and supervision by NTP staff to ensure that quality outcomes are maintained.
- Selection of community volunteers should be a cooperative activity including NTP staff, TB patients, community representatives and community group leaders.

- Training requirements may vary depending on the setting, ranging from “on the job instruction” by NTP staff to more formal short courses of instruction supported by regular updates.
- Regular audit and reporting of results are important to define and clarify the community contribution to TB care in each programme.

6.3.6 *How should directly observed treatment be applied in different settings?*

Implementation of DOT depends on the setting, facilities, resources and environment. There must therefore be flexibility in applying directly observed treatment, with adaptation in different districts and countries. Major factors influencing treatment interruption are access to treatment (distance, cost of transport, time and wages lost, quality and speed of drug delivery), levels of knowledge about TB and the need to complete treatment, and flexibility for transfer to another facility. Thrice-weekly regimens reduce the onus on patients and staff, and free staff on alternate days to locate patients who did not present for treatment.

For any chosen method of supervision and administration of treatment, a programme must show high sputum smear conversion and cure rates, under routine conditions, in both rural and urban areas. If evaluation of the method of supervision and administration of the regimen showed that the method failed, it should be altered and tested in regional and national demonstration and training districts.

A district or region that demonstrates a successful method of implementing DOT can serve as a model for other districts or regions. A country that demonstrates successful implementation of directly observed treatment might be a model for neighbouring countries in the same region.

6.4 *Interruption of treatment: what to do?*

Directly observed treatment adapted to the needs of patients and to the working conditions of health care workers is certainly the best method of avoiding treatment interruption. However, even with directly observed treatment, and also during the continuation phase of treatment that is often self-administered, there may be treatment interruptions.

6.4.1 *Preventive measures to minimize treatment interruption*

At the time of registration of a TB patient starting treatment, sufficient time should be set aside to meet with the patient (and preferably also with the patient’s family members). This initial meeting provides an important opportunity to advise and counsel the patient. During the meeting, it is vital to record the patient’s address and other relevant addresses (e.g. partner or spouse, parents, work place, place of study) in order to maximize the probability of locating patients who interrupt treatment. Where resources permit, it is helpful for a health

staff member to accompany the patient to their residence following the initial meeting. It is also important to identify potential problems that the patient may face during the initial phase of treatment. Health staff must inform the patient about the duration of treatment, and the need to consult ahead of time in case of permanent or temporary change of address, to facilitate continuation of treatment.

In the meeting at the end of the initial phase of treatment, the patient can inform the health worker about plans (work, family, moving house) for the following months of the continuation phase of treatment. In some countries, a visit to the patient's home before or during the initial phase of treatment allows verification of the exact address, and at the same time provides an opportunity to arrange for screening of household contacts, especially children aged under 5 years.

All visits of the patient to the clinician should reinforce the need for regular and complete intake of treatment and elicit any problems that may cause interruption.

6.4.2 *Corrective measures to minimize the duration of treatment interruption*

Enquiries should be made about any patient who misses an arranged appointment to receive treatment, using the contact addresses previously obtained and appropriate means of tracing. It is important to find out the cause of the patient's absence in order to take appropriate action and continue treatment. The patient should be contacted the next day after missing treatment during the initial phase and within a week during the continuation phase.

6.4.3 *What should be done when a patient returns after interrupting treatment?*

The management of patients who have interrupted treatment is complex and takes into consideration several variables (immune status, degree of remission of the disease with the previous treatment, drug susceptibility) that may be difficult to assess. A simple decision tree is suggested in Table 6.1. More detailed decision trees can be used but require further training.

Table 6.1 Actions in interruption of TB treatment

Interruption for less than 1 month			
<ul style="list-style-type: none">Trace patientSolve the cause of interruptionContinue treatment and prolong it to compensate for missed doses			
Interruption for 1–2 months			
Action 1		Action 2	
<ul style="list-style-type: none">Trace patientSolve the cause of interruptionDo 3 sputum smears. Continue treatment while waiting for results.	If smears negative or EPTB	Continue treatment and prolong it to compensate for missed doses	
	If one or more smears positive	Treatment received: <5 months	Continue treatment and prolong it to compensate for missed doses
		>5 months	Category I: start Category II Category II: refer (may evolve to chronic)
Interruption for 2 months or more (defaulter)			
<ul style="list-style-type: none">Do 3 sputum smearsSolve the cause of interruption, if possibleNo treatment while waiting for results	Negative smears or EP	Clinical decision on individual basis whether to restart or continue treatment, or no further treatment	
	One or more smears positive	Category I	Start Category II
		Category II	Refer (may evolve to chronic)

Suggestions for further reading

Community TB care in Africa: a collaborative project coordinated by WHO. Geneva, World Health Organization, 2001 (document WHO/CDS/TB/2001.291).

Pio A, Chaulet P. Tuberculosis handbook, 2nd ed. Geneva, World Health Organization, 2003. (document WHO/CDS/TB/2003.320).

Training modules for health facility staff. Geneva, World Health Organization, 2002 (document WHO/CDS/TB/2003.314a–k).

7 MONITORING THE PATIENT

7.1 Objectives of chapter

The objectives of this chapter are to provide clear guidelines on:

- how to monitor and record the response to treatment, especially in sputum smear-positive TB patients;
- how to monitor and manage drug-induced toxicity.

7.2 Monitoring the treatment response

Patients with sputum smear-positive pulmonary TB should be monitored by sputum smear examination. These are the patients for whom bacteriological monitoring is possible. It is unnecessary, unreliable and wasteful of resources to monitor patients by chest radiography. For patients with sputum smear-negative PTB and EPTB, clinical monitoring is the usual way of assessing the response to treatment. Under programme conditions in countries with a high incidence of TB, routine monitoring by sputum culture is not feasible or recommended. Culture can be used to confirm or reject treatment failure and to determine the drug susceptibility pattern in failure cases.

7.3 New sputum smear-positive pulmonary TB patients (Category I)

Response to treatment should be monitored by sputum smear examination. In general, two sputum specimens should be collected for smear examination at each follow-up sputum check. Sample collection should be done without interrupting treatment.

Sputum smears should be performed at the end of the second month, during the fifth month and in the last month of the 6-month and 8-month treatment regimens. Negative sputum smears indicate good treatment progress, which encourages the patient and the health worker responsible for supervising treatment.

At the end of the second month of treatment, most patients will have a negative sputum smear and will then start the continuation phase of treatment. If a patient has a positive sputum smear at this time, this may indicate one of the following:

- most frequently, that the initial phase of therapy was poorly supervised and that patient adherence was poor;
- sometimes, that there is a slow rate of progress with sputum smear conversion, e.g. if a patient had extensive cavitation and a heavy initial bacillary load;
- rarely, that the patient may have drug-resistant TB that does not respond to first-line treatment.

Whatever the reason, if the sputum smears are positive at the end of the second month, the initial phase is prolonged for a third month. The patient then starts the full continuation phase. Smears may be checked at the end of the third month to evaluate smear conversion in the cohort. If the sputum smears are still positive during the fifth month, this constitutes treatment failure. The patient is reregistered as a treatment failure and starts a full course of re-treatment regimen, either with a Category II or a Category IV regimen with reserve drugs (see Chapter 5). Countries where culture is routinely available may use it to confirm treatment failure before starting re-treatment. However, this may result in delays of 2 months or more, with increased transmission and deterioration of smear-positive culture-positive cases.

In most countries with high TB prevalence, susceptibility testing should be reserved for surveillance of drug resistance. Access to culture facilities and the reliability of and opportunity for susceptibility testing are usually inadequate for the use of susceptibility test results in patient management. In some settings where culture facilities are accessible and susceptibility test results are reliable, susceptibility testing can be useful in cases of treatment failure or relapse and, in chronic cases, to select an individually tailored treatment regimen (see section 7.4 and Chapter 5).

7.4 Previously treated pulmonary sputum smear-positive patients (Category II)

Sputum smear examination is performed at the end of the initial phase of treatment (at the end of the third month), during the continuation phase of treatment (second month after starting continuation) and at the end of treatment. If the patient is sputum smear-positive at the end of the third month, the initial phase of treatment with 4 drugs is extended by another month and sputum smears are examined again at the end of the fourth month. If the patient still has positive smears at the end of the fourth month, sputum is sent to the laboratory for culture and sensitivity testing, where possible, and the patient then starts the continuation phase. If the culture and sensitivity results show resistance to 2 of the 3 drugs employed in the continuation phase, the patient should be referred to a specialized centre for consideration of treatment with reserve antituberculosis drugs. Where there are no facilities for culture and sensitivity testing, the patient continues treatment right until the end of the re-treatment regimen. Positive smears at the end of the fifth month indicate failure of the re-treatment regimen and, if a standard regimen for chronic and drug resistant patients is available, the patient should be referred.

7.5 New sputum smear-negative pulmonary TB patients (usually Category III)

Sputum smear-negative patients should be monitored clinically; body weight is a useful progress indicator.

Sputum smears should be checked at the end of the second month in case of the following possibilities: disease progress due to non-adherence to treatment, or an error at the time of initial diagnosis (i.e. a true smear-positive patient misdiagnosed as smear-negative) plus drug resistance. A patient initially diagnosed as sputum smear-negative and treated as a Category III patient who has positive sputum smears (two positive samples, to reduce errors) at the end of the second month should start a full course of Category II treatment. The outcome of the initial treatment should be failure and the patient should be reregistered. (Note that this is an exception, as failure for initially smear-positive patients is defined as sputum smear-positive at the end of the fifth month of treatment or later.)

7.6 Extrapulmonary TB

Response to treatment can be monitored only through clinical observation. As in pulmonary smear-negative disease, the weight of the patient is a useful indicator.

7.7 Recording standardized treatment outcomes

At the end of the treatment course for each patient with sputum smear-positive PTB, the District TB Officer records the treatment outcome in the District TB Register. Table 7.1 shows the definitions of standardized treatment outcomes.

Table 7.1 Recording treatment outcome in smear-positive TB patients

Cure	Patient who is sputum smear-negative in the last month of treatment and on at least one previous occasion.
Treatment completed^a	Patient who has completed treatment but who does not meet the criteria to be classified as a cure or a failure.
Treatment failure	Patient who is sputum smear-positive at 5 months or later during treatment. ^b
Died	Patient who dies for any reason during the course of treatment.
Default	Patient whose treatment was interrupted for two consecutive months or more.
Transfer out	Patient who has been transferred to another recording and reporting unit and for whom the treatment outcome is not known.

^a Treatment success is defined as the sum of patients cured and those who have completed treatment.

^b Also a patient who was initially smear-negative before starting treatment and became smear-positive after completing the initial phase of treatment.

7.8 Cohort analysis of treatment outcome in smear-positive pulmonary TB patients

A cohort is a group of patients diagnosed and registered for treatment during a specific time period (usually 3 months). Evaluation of treatment outcome in new pulmonary smear-positive patients is used as a major indicator of programme quality. Outcome in other patients (re-treatment, pulmonary smear-negative, extrapulmonary) may also be analysed, in separate cohorts.

Cohort analysis is the key management tool for evaluating the effectiveness of the NTP. It allows the identification of problems, so that the NTP can institute appropriate action to overcome them and improve programme performance. Evaluation of the results of treatment and trends must be done at peripheral, district, regional and national level if corrective action is to be taken.

The District TB Officer should perform cohort analysis of treatment outcome every 3 months and at the end of every year. A typical cohort consists of all those new pulmonary sputum smear-positive TB patients registered during a quarter (i.e. 1 January to 31 March, 1 April to 30 June, 1 July to 30 September, and 1 October to 31 December). New and previously treated patients (relapses, return after default, failures) should be analysed as separate cohorts, because they have different characteristics and expected results. Evaluation of outcome at the end of treatment takes place about three months after all patients in the cohort have time to complete their course of treatment.

Transmission of this information is done in quarterly reports. District quarterly reports on treatment outcome are forwarded to the region. The Regional TB Officer should verify that district reports are correct, complete and consistent, compile cohort analysis reports on the sputum smear-positive patients in the region, and submit the report to the central unit of the NTP. The NTP compiles cohort analysis reports on the smear-positive TB patients registered nationally, evaluates and provides feedback to the programme staff.

7.8.1 Cohort analysis of treatment outcome in chronic and MDR-TB patients

Outcome evaluation of chronic and MDR-TB cases need special cohort analysis. Analysis takes place at the end of treatment (21–24 months) and 6 months later, at 30 months. At least two sub-cohorts must be analysed:

- patients treated with a standard Category IV regimen, according to the national procedures;
- patients treated with individualized Category IV regimens, according to the available drug susceptibility testing results.

7.9 Monitoring of TB patients for significant adverse effects of antituberculosis drugs

Most TB patients complete their treatment without any significant adverse effects of drugs. However, a few patients do experience adverse effects. It is therefore important that patients be clinically monitored during treatment so that adverse effects can be detected promptly and managed properly. Routine laboratory monitoring is not necessary.

Health personnel can monitor adverse effects of drugs by teaching patients how to recognize symptoms of common adverse effects and to report if they develop such symptoms, and by asking about symptoms when patients report to collect drugs.

7.10 Prevention of adverse effects of drugs

Health personnel can prevent some drug-induced side-effects, for example isoniazid-induced peripheral neuropathy. This usually presents as a numbness, tingling or burning sensation of the feet and occurs more commonly in pregnant women and in people with the following conditions: HIV infection, alcohol abuse, malnutrition, diabetes, chronic liver disease. These patients should receive preventive treatment with pyridoxine, 10 mg daily, along with their antituberculosis drugs.

7.11 Adverse effects of antituberculosis drugs

The adverse effects of essential antituberculosis drugs are described in Annex 2 and of reserve drugs in Annex 3. Table 7.2 shows a symptom-based approach to the most common adverse effects of the essential antituberculosis drugs. Adverse effects are classified as minor or major. In general, a patient who develops minor adverse effects should continue the TB treatment, sometimes at a reduced dose. The patient also receives symptomatic treatment. If a patient develops a major side-effect, the treatment or the offending drug is stopped. Further management depends on the nature of the adverse reaction. Patients with major adverse reactions should be managed in a hospital.

Table 7.2 Symptom-based approach to side-effects of antituberculosis drugs^a

SIDE-EFFECTS	DRUG(S) PROBABLY RESPONSIBLE	MANAGEMENT
Minor		Continue anti-TB drugs, check drug doses
Anorexia, nausea, abdominal pain	Pyrazinamide, rifampicin	Give drugs with small meals or last thing at night
Joint pains	Pyrazinamide	Aspirin
Burning sensation in the feet	Isoniazid	Pyridoxine 100 mg daily
Orange/red urine	Rifampicin	Reassurance. Patients should be told when starting treatment that this commonly happens and is normal
Major		Stop responsible drug(s)
Itching, skin rash	Thioacetazone (S, H, R, Z)	Stop anti-TB drugs, (see below)
Deafness (no wax on auroscopy)	Streptomycin	Stop streptomycin, use ethambutol
Dizziness (vertigo and nystagmus)	Streptomycin	Stop streptomycin, use ethambutol
Jaundice (other causes excluded) hepatitis	Isoniazid, pyrazinamide, rifampicin	Stop anti-TB drugs, (see below)
Confusion (suspect drug-induced acute liver failure if jaundice present)	Most anti-TB drugs	Stop anti-TB drugs. Urgent liver function tests and prothrombin time
Visual impairment (other causes excluded)	Ethambutol	Stop ethambutol
Shock, purpura, acute renal failure	Rifampicin	Stop rifampicin

^a Side-effects of reserve drugs are described in detail in *Guidelines for establishing DOTS-Plus pilot projects for the management of multidrug-resistant tuberculosis (MDR-TB)*. Geneva, World Health Organization, 2000 (document WHO/CDS/TB/2000.279).

7.11 Management of a cutaneous reaction

Management of a cutaneous reaction depends on whether or not the patient is receiving thioacetazone.

Treatment regimen includes thioacetazone

If a patient develops pruritus, with or without a rash, and there is no other obvious cause (e.g. scabies), antituberculosis drugs should be stopped immediately. If there is severe rash, or if there is mucosal involvement or hypotension, the patient will need intravenous fluids, and possibly steroids. Treatment is restarted only when the rash has resolved, replacing thioacetazone with ethambutol. A patient must never receive thioacetazone again after any thioacetazone reaction.

Treatment regimen does not include thioacetazone

If a patient develops itching and there is no other obvious cause (e.g. scabies), the recommended approach is to try symptomatic treatment with antihistamines, reassurance and avoiding dry skin, continue TB treatment and observe the patient closely. However, if a skin rash develops all antituberculosis drugs must be stopped. Once the reaction has resolved, antituberculosis drugs are reintroduced. The problem is how to reintroduce TB treatment when the particular TB drug responsible for the reaction is not known.

The idea of drug challenging is to identify the drug responsible for the reaction. Drug challenge starts with the antituberculosis drug least likely to be responsible for the reaction (i.e. isoniazid). The idea of starting with a small challenge dose is that if a reaction occurs to a small challenge dose, it will be less severe than the reaction to a full dose. The dose is gradually increased over three days. The procedure is repeated, adding in one drug at a time. A reaction after adding in a particular drug identifies that drug as the one responsible for the reaction. There is no evidence that this challenge process gives rise to drug resistance. If the drug responsible for the reaction is pyrazinamide, ethambutol or streptomycin, TB treatment is resumed without the offending drug. If possible, the offending drug is replaced with another drug. It may be necessary to extend the treatment regimen. This prolongs the total time of TB treatment, but decreases the risk of relapse.

The reader is referred to *Clinical tuberculosis*¹ for details.

7.11 Management of drug-induced hepatitis

Most antituberculosis drugs can damage the liver. Isoniazid, pyrazinamide and rifampicin are most commonly responsible, ethambutol rarely. When a patient develops hepatitis during TB treatment, the cause may be the TB treatment or something else. It is important to rule out other possible causes before deciding that the hepatitis is drug-induced. If the diagnosis is drug-induced hepatitis, the antituberculosis drugs should be stopped. The drugs must be withheld until liver function tests have reverted to normal. Sometimes it is not possible to perform liver function tests; in these situations, it is advisable to wait an extra 2 weeks after the jaundice has disappeared before recommencing TB treatment. Asymptomatic jaundice without evidence of hepatitis is probably due to rifampicin. Once drug-induced hepatitis has resolved, the same drugs are reintroduced one at a time. However, if the hepatitis produced clinical jaundice, it

¹ Crofton J, Horne N, Miller F. *Clinical tuberculosis*, 2nd ed. London, Macmillan Educational Limited, 1999.

is advisable to avoid pyrazinamide. A suggested regimen in such patients is a 2-month initial phase of daily streptomycin, isoniazid and ethambutol, followed by a 10-month continuation phase of isoniazid and ethambutol (2 SHE/10 HE). A severely ill TB patient with drug-induced hepatitis may die without antituberculosis drugs. In this case, the patient should be treated with two of the least hepatotoxic drugs, streptomycin and ethambutol. After the hepatitis has resolved, usual TB treatment should be restarted.

Suggestions for further reading

Pio A, Chaulet P. Tuberculosis handbook, 2nd ed. Geneva, World Health Organization, 2003. (document WHO/CDS/TB/2003.320).

8

TUBERCULOSIS IN CHILDREN**8.1 Objectives of chapter**

This chapter describes the epidemiology, clinical presentation and management of TB in children.

8.2 Epidemiology

Children are usually infected with tuberculosis by an adult or an older child with sputum smear-positive PTB, often a family member. Less commonly, they may be infected by contact with smear-negative (often culture-positive) cases. The best way to prevent childhood TB is therefore by proper identification and treatment of infectious patients. Case notifications of childhood TB usually represent 6-20% of all TB cases registered with the NTP. Children can present with TB at any age, but the most common age is between 1 and 4 years. The frequency of childhood TB depends on the intensity of the epidemic, the age structure of the population, the available diagnostic tools and whether contact tracing is routinely undertaken. The ratio of PTB:EPTB in children is usually around 1:3 but varies depending on factors such as age, ability to examine contacts and possibly genetic factors.

Children may also be infected with *Mycobacterium bovis* by drinking untreated milk from infected cows. They often present with cervical TB adenitis or intestinal TB but can also develop PTB or disseminated disease.

The risk of infection in children depends on the extent of exposure to infectious droplet nuclei. For example, if a mother has sputum smear-positive PTB, her infant is more likely to become infected because of the very close contact and the higher risk of inhaling a large number of infectious droplets. The greater the exposure to infection, the greater the likelihood of disease.

The majority of infected children do not develop TB disease in childhood. The only evidence of infection may be a positive tuberculin skin test. The likelihood of developing disease is greatest shortly after infection and declines steadily with time. Infants and young children aged under 5 years are at particular risk of developing disease. If an infected child does develop disease, the majority will present with symptoms within one year of infection. For infants particularly, the time-span between infection and disease may be as little as 6-8 weeks. Various immunosuppressive illnesses may facilitate progression of infection to disease, including HIV infection, measles, whooping cough and protein-calorie malnutrition. These conditions are also most common in infancy and early childhood.

8.3 Clinical presentation and diagnosis

The commonest type of TB in children is EPTB, mainly intrathoracic. Common forms of EPTB in children include TB lymphadenopathy, TB meningitis, TB

effusions (pleural, pericardial and peritoneal) and spinal TB. The diagnosis of respiratory TB in children is difficult because there is some confusion between primary infection (often without obvious lesions in the lungs) and PTB. Pulmonary TB is usually smear-negative. This is because many children present with primary rather than reactivation (cavitary) PTB and because the majority of children with PTB are too young to produce sputum for smear microscopy. Smear-positive PTB is usually diagnosed in school-aged children. The prevalence of PTB is normally low between the ages of 5 and 12 years and then increases slightly again in adolescence, when PTB presents more like adult PTB (i.e. with cavitation).

The presentations of TB in children are:

- **Primary TB disease¹**

- Often **unilateral lymphadenopathy**, hilar or mediastinal, without radiographic abnormalities in the lung (no obvious parenchymal involvement). It is the most frequent (70-80%) and should be classified as EPTB and treated as Category III.
- Sometimes **typical “primary complex”**, combining hilar/mediastinal lymphadenopathy and a small opacity in the lung, 3-10 mm in diameter (“primary lesion”). It is less frequent (20%, usually in children aged under 5 years). This is classified as a case of PTB and should be treated as Category III.
- Rarely, **lobar or segmental opacity** in the lung, combined with unilateral lymphadenopathy on the same side. A PTB case with large parenchymal involvement should be treated as Category I. When bronchial compression has resulted in atelectasis, corticoids in addition to chemotherapy may be helpful. Cavitation of the primary lesion in the lung is exceptional in children, and is classified as PTB, often smear-positive.

- **Acute disseminated post-primary TB** (often in children aged under 5 years): miliary with or without meningitis. Classified as severe extrapulmonary, Category I.
- **Post-primary PTB** (usually in children aged over 10 years): without cavitation, smear-negative or with cavitation, smear-positive. Category I.
- **Post-primary EPTB:** Category I or III.

8.3.1 *Approach to diagnosis*

The diagnosis of PTB is difficult in children aged under 6-8 years, particularly in the low-resource setting. Important features include:

- contact with a smear-positive PTB case;
- respiratory symptoms for more than 2-3 weeks, not responding to broad-spectrum antibiotics;

¹ Symptomatic primary disease is rarely observed with normal X-ray; diagnosis is more commonly based on clinical signs such as erythema nodosum and phlyctenular keratoconjunctivitis.

- weight loss or failure to thrive;
- positive test to the standard dose of tuberculin (2 TU of RT23 or 5 TU of PPD-S): 10 mm or more in unvaccinated children, 15 mm or more in BCG-vaccinated children; however, with severe TB and/or advanced immunosuppression, the tuberculin test may be negative in infected persons.

There are no specific clinical findings for a diagnosis of PTB. There may be clues to other diagnoses such as asthma, bronchiectasis, whooping cough, inhaled foreign body or cardiac disease. Diagnosis of childhood PTB requires chest X-ray (CXR), although CXR findings are often not specific and certainly not diagnostic. Upper and mid-lobe infiltrates are more common, cavitory disease is uncommon. The usefulness of the tuberculin test and CXR are further reduced in malnourished or HIV-infected children, yet these are common conditions that often need to be differentiated from TB. However, radiographic and clinical findings suggestive of TB become more specific when it has been established that the child has been in close contact with a diagnosed case of PTB, especially smear-positive PTB.

The effort to establish a positive contact history deserves special emphasis. A positive history increases the likelihood that the child does indeed have TB. It may also lead to identification of a previously undiagnosed infectious case. History should therefore include specific enquiry about any symptoms, especially cough, of living or recently deceased household members.

The readily available usual test for adults and older children with PTB, sputum smear microscopy, is not possible for the majority of young children, who usually swallow their sputum. Other methods of obtaining material, such as gastric lavage, can be problematic to implement as a routine diagnostic procedure, are less sensitive and generally not useful unless facilities are available for *M. tuberculosis* culture. This means that bacteriological confirmation is usually not possible and that the diagnosis of PTB in children is often presumptive. Scoring systems have been produced for screening and diagnostic purposes, but their evaluation is difficult in the absence of a “gold standard” diagnosis. They are likely to be even less accurate in regions where childhood malnutrition and HIV infection are common. A “trial of TB treatment” should not be used as a diagnostic manoeuvre.

The diagnosis of EPTB in children is usually more straightforward because of characteristic clinical features (e.g. spinal deformity, scrofula or painless ascites) and, infrequently, supportive microscopic findings on specimens such as cerebrospinal fluid, pleural fluid, ascitic fluid and lymph node aspiration or biopsy.

8.3.2 *Tuberculin skin test*

A positive tuberculin test does not indicate the presence or extent of tuberculosis disease; it only indicates infection. In a child who has not had BCG, a tuberculin test is defined as “positive” when the diameter of skin induration is 10 mm or more. In a child who has had BCG, an induration of 10-14 mm may be due to

vaccination or TB infection. A negative tuberculin skin test does not exclude TB infection and some induration, e.g. 5-14 mm, is supportive if the clinical features and contact history are suggestive. The tuberculin test is less likely to be positive in a child with TB if the child also has severe malnutrition, HIV infection or disseminated TB such as miliary disease or TB meningitis.

8.3.3 *Impact of HIV on diagnosis of TB in children*

HIV makes diagnosis and management of TB in children more difficult for the following reasons:

- Other HIV-related disease, such as lymphocytic interstitial pneumonitis, may present in a similar way to PTB or miliary TB.
- Interpretation of tuberculin skin testing and CXR is less reliable.
- When TB/HIV coinfection is common in adults, a positive contact history is less specific if the contact is the child's parent. The child is at risk of transmission of either or both diseases.
- Children with TB and advanced HIV disease may not respond as well to TB treatment.

HIV testing can be helpful, especially if the result is negative, as it increases the likelihood of a diagnosis of TB. However, a positive HIV result clearly does not exclude the possibility of TB.

8.4 **Management of childhood TB**

The DOTS strategy is applicable to all patients with tuberculosis, including children. High success rates (over 95%) are achievable in children with PTB and less severe forms of EPTB such as TB lymphadenopathy. Thioacetazone can cause severe and often fatal reactions in HIV-infected children and so should not be used in HIV-endemic regions. It has been replaced by ethambutol. There has been understandable caution with the use of ethambutol in children too young to report early visual deterioration, but ethambutol has been safely used in infants and young children at recommended dosages.

The recommended treatment regimens and dosages for the treatment of childhood TB are the same as for adults (see Chapter 4 and Table 8.1). This is because uniformity is likely to reduce confusion and therefore improve overall compliance - important from the NTP perspective. However, there are important differences between children and adults that may affect drug choice and dosage. Recommended dosages are based on research in adults and yet metabolism of drugs varies with age. The effectiveness of the recommendation of EH for the maintenance or continuation phase has never been studied in children, whereas RH has proven efficacy. Mortality is high and long-term sequelae common with TB meningitis - the best prevention is rapid diagnosis and treatment. In children

with TB meningitis, streptomycin (or ethionamide) should be used instead of ethambutol because ethambutol does not cross the blood-brain barrier. Corticosteroids are sometimes useful in TB meningitis or in lobar/segmental opacity due to a lymphadenopathy.

The drug dosages per kilogram are the same for children and adults (see section 4.3 and Table 4.1.)

Table 8.1 Recommended regimens for treatment of tuberculosis in children

CLINICAL PRESENTATION	CATEGORY AND TREATMENT REGIMEN
Sputum smear-positive PTB Sputum smear-negative TB with extensive parenchymal involvement (acute military, segmental/lobar opacity) Severe EPTB (disseminated acute TB, abdominal, spinal and pericardial TB)	Category I 2 RHZE/4 RH daily or 3 times weekly
TB meningitis	Category I 2 RHZS/4 RH
Sputum smear-negative PTB Less severe EPTB (TB adenitis, mediastinal lymphadenopathy)	Category III 2 RHZ/4 RH daily or 3 times weekly

8.5 Management of child contacts of infectious adults

Active tracing of children who are household contacts of smear-positive PTB cases is recommended. Ideally, screening should include at least a thorough history, clinical examination, tuberculin test, CXR and HIV test. Those with a diagnosis of TB are then treated. Those who are well and aged under 5 years should receive prophylaxis (isoniazid 5 mg/kg daily). This will significantly reduce the likelihood of their developing TB disease. Breastfeeding children of a sputum smear-positive mothers are the most important group for preventive therapy. Prophylaxis should be for at least 6 months and requires regular (e.g. every 2 months) follow-up. Children aged over 5 years who are well do not require prophylaxis, only clinical follow-up.

Children may also be infected by smear-negative PTB cases but, because transmission is less common, routine contact tracing is not recommended in this circumstance.

Suggestions for further reading

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ANTITUBERCULOSIS DRUG SUPPLY AND USE

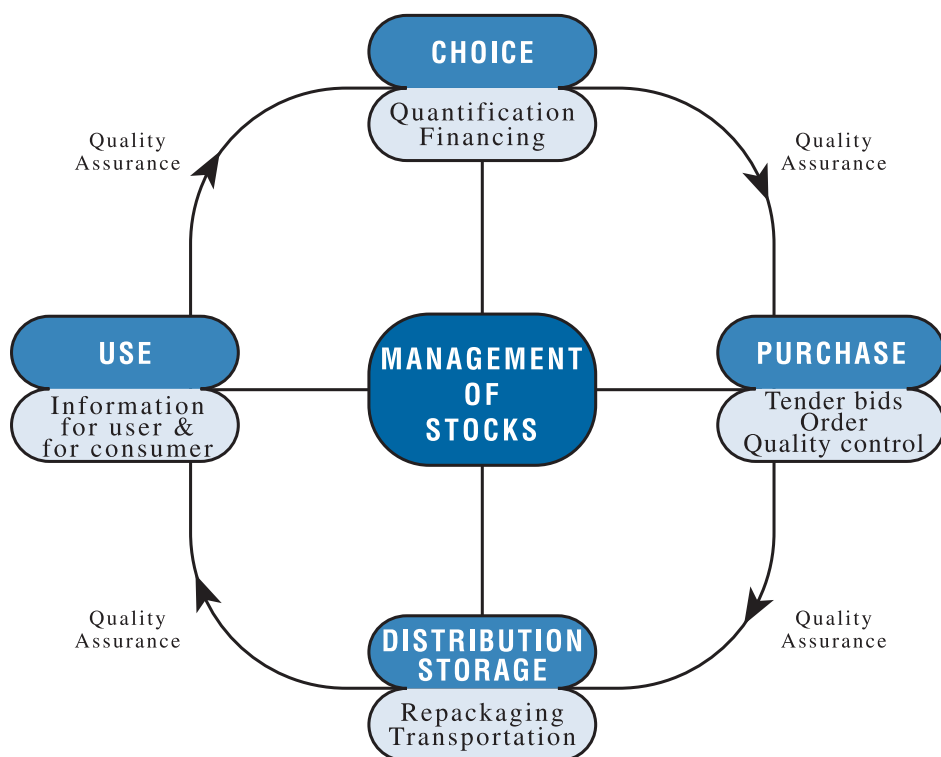
9.1 Objectives of chapter

Prerequisites for the success of all NTPs include a regular supply of antituberculosis drugs and appropriate use of the drugs. The essential task of NTP managers is always to ensure a complete curative course of chemotherapy for all detected and registered TB patients. This chapter sets out how NTP managers can ensure a regular supply of antituberculosis drugs and appropriate use of the drugs.

9.2 The drug logistic cycle

To accomplish the task of ensuring the regular supply of antituberculosis drugs and their appropriate use, each step of the drug logistic cycle must be followed (Figure 9.1). The last and most crucial step, regular and complete intake of the correct treatment by the patient is addressed in Chapters 4, 5 and 6. Monitoring of the results is dealt with in Chapter 7.

Figure 9.1 Drug logistic cycle



9.3 Selecting the appropriate drug formulations

Selection of the appropriate formulations of the essential antituberculosis drugs is one of the most important responsibilities of national programme officials, and may require the assistance of consultants. The aim of their choice is to:

- facilitate prescription of standardized chemotherapy
- obtain better purchase prices by limiting the number of formulations adopted
- simplify supplies and stock management
- facilitate drug quality control.

The choice of the appropriate formulations depends on the chemotherapy regimen chosen by the national programme. Short-course regimens (6 or 8 months) have replaced the former 12- to 18-month regimens, which were longer, less efficacious and contained no rifampicin.

Short-course chemotherapy may be administered daily or 3 times weekly, thus facilitating directly observed treatment. It may also be administered daily during the initial phase of treatment, then thrice weekly during the continuation phase. In some countries, there are geographical areas or groups of patients for whom two types of standardized short-course chemotherapy may be chosen: one of them daily, the other wholly or partly intermittent.

The WHO Model List of Essential Drugs indicates formulations that meet a large range of national programme needs, either in the form of separate drugs or as fixed-dose combinations (see Table 4.2). Other formulations may be adopted by certain national programmes, provided that the bioavailability of the components - in particular rifampicin in fixed-dose combinations - has been demonstrated.

Several fixed-dose combinations of 2, 3 and 4 antituberculosis drugs are available on the market. Both WHO and the International Union Against Tuberculosis and Lung Disease (IUATLD) stress that these combinations may only be fully efficacious if they contain the correct dose of each prescription drug and each component is fully absorbed. A number of studies have shown some combinations to be incorrect or incompletely absorbed. WHO and IUATLD therefore recommend that use of these fixed-dose combinations be restricted to combinations whose bioavailability has been demonstrated by laboratories that are independent from the manufacturers.

The essential advantage of fixed-dose combinations of 2, 3 or 4 drugs is to prevent monotherapy (use of one drug). They also offer other operational advantages: preventing errors of prescription and dosage, simplifying the standardization of chemotherapy regimens, facilitating information to patients and health workers, acceptance and compliance by patients, avoiding stock-outs of a single drug, improving management and distribution, and simplifying needs assessment by programme officials. The use of fixed-dose combinations of isoniazid plus rifampicin is essential to reduce the risk of monotherapy with these

bactericidal drugs, and of isoniazid plus ethambutol because they are self-administered in the second phase of treatment.

The use of fixed-dose combinations does not preclude the need to purchase and stock limited amounts of separate drugs for use in special regimens for persons with drug toxicity or special requirements.

Whatever the formulations chosen, the NTP manager must ensure that these formulations are included in the national essential drugs list.

9.4 Choice of packaging

In recent years, the choice of packaging for antituberculosis drugs has become a major factor determining the success of programmes in the field.

Drugs (whether separate or in combination) may be supplied in 500-, 1000- or 10 000-tablet containers; the advantage of this form of packaging is that it reduces prices. The drawback is the need for handling operations when the drugs are distributed to patients; the drugs are counted by hand - not always in hygienic conditions - and put into paper or plastic bags. There is a greater chance of errors, and light, heat or humidity may affect the drugs. Drugs may also be supplied as separate tablets in either blister packs or strips. Provided that the plastic or aluminium used to package the drugs is of good quality, the drugs are better protected and preserved.

The choice of packaging may influence the system of distribution, which needs to be suited to the situation in each country, depending on population density, health coverage and the skills of the health workers responsible for distribution.

Blister packs containing a day or a week's drug supply (either separate or combined) are a very practical form of packaging, especially for the initial phase of treatment. Strips containing the combination of drugs necessary for one week's or one month's treatment are a practical form of packaging for the continuation phase.

In some countries, all the drugs necessary for a full course of treatment may be placed in a "box" corresponding to the patient's weight, which is delivered to the peripheral health centre. This procedure makes it easier to distribute drugs and to monitor the regularity of treatment and prevents supply breakdowns for the individual patient. The patient boxes can also be prepared in the health centre. All these options need to be studied in order to facilitate programme implementation in peripheral areas.

9.5 Determining the appropriate quantities of each drug or combination of drugs

A more complex task than selecting the drugs is deciding on the quantities needed. Calculation of these quantities should be based on the number of cases in

the different treatment categories notified the previous year, the standardized treatment regimens used in the NTP, and the existing and required stocks. It is essential to plan for reserve stocks for each level, e.g. 3 months at district level, 3 months at provincial level, 6 months at central level. Practical methods to quantify drug needs are fully described in the *Tuberculosis handbook*.¹

A more precise estimate is required if different formulations are used, depending on the patients' age and weight. As a rule, weight categories should be limited to 2-4 for adult patients, and the number of children among TB patients should be taken into account.

9.6 Ensuring the quality of antituberculosis drugs

Good quality assurance and control of pharmaceuticals is of crucial importance in both medical and commercial terms. The quality of drugs (separate and especially combined tablets) to be used in TB control should be assured before purchase and through regular quality assessment of batches received by periodic random sampling at all levels.

A model protocol has been drawn up for evaluating the bioavailability of rifampicin in fixed-dose combinations. The protocol is applicable in national control laboratories (when they exist) or in a supranational network of WHO-approved laboratories, independent from manufacturers.

The quality of drugs depends upon a set of standards being maintained throughout the entire process of manufacture and distribution. This calls for adequate regulation, an inspection system and quality-control facilities. Weak regulation and poor enforcement can lead to the presence of counterfeit and substandard drugs on the market.

National TB control programmes should ensure that antituberculosis drugs are of good quality by making sure that the drugs:

- are produced following the good manufacturing practices recommended by WHO;
- are imported with a WHO certificate (WHO's certification scheme on the quality of pharmaceutical products moving in international commerce);
- when bought by competitive tender, are ordered with the appropriate specifications;
- are stored properly following good storage practice and the FIFO² principle.

9.7 Financing and procuring of antituberculosis drugs

Better systems of procurement, access to market information and bulk orders can achieve considerable savings. The best way to obtain drugs of good quality at low

¹ Pio A, Chaulet P. *Tuberculosis handbook*, 2nd ed. Geneva, World Health Organization, 2003 (document WHO/CDS/TB/2003.320).

² first in, first out.

cost is through competitive tender for bulk drugs in standard packages. Using International Nonproprietary Names for pharmaceutical substances is essential to standardize drug procurement.

Annex 5 presents the cost of the essential antituberculosis drugs according to the most recent Management Sciences for Health price list and the cheapest price available through the Global Drug Facility (GDF) in 2002.

The cost of antituberculosis drugs has fallen considerably over the past 10 years. Today, the cost of the necessary drugs for a short-course regimen of 6 or 8 months is between US\$ 10 and US\$ 20 for the first-line regimen, and between US\$ 15 and US\$ 30 for the re-treatment regimen. The availability of essential antituberculosis drugs and supplies can be ensured in most countries with high TB prevalence for less than 10 US cents per inhabitant.

Countries can have access to competitively priced antituberculosis drugs through the GDF, an international mechanism to ensure access to high-quality essential antituberculosis drugs for DOTS expansion. The GDF has established a direct procurement mechanism, whereby governments or organizations are able to use their own or donor finances to purchase quality antituberculosis drugs at concessionary prices. Further information is available on the web at <http://www.globaldrugfacility.org> and http://www.stoptb.org/GDF/drugsupply/Direct_procurement_process.html. Countries can also apply to the GDF for grants of free antituberculosis drugs via a formal applications procedure.

Drugs for the treatment of one chronic case are much more expensive - US\$ 2000-6000 per patient in low- to middle-income countries. Reserve drugs can be obtained at competitive prices through WHO, by submitting a project for management of chronic cases to the GLC. Further information is available on the web at <http://www.who.int/gtb/policyrd/DOTSplus.htm>.

Countries or organizations able to estimate their long-term drug needs can purchase supplies in bulk and/or with a long-term contract (3 years for instance). By joint procurement at inter-country or regional level, countries and/or organizations are also able to buy the drugs at lower prices in the global market through lower price suppliers or procurement agencies.

When calculating and projecting real costs for the programme, it is important to consider factors such as financing, delivery times, insurance, modes of transportation (air/sea/overland) and handling charges. These factors should be carefully analysed in each country: for instance, according to the country, the CIF¹ price is obtained by adding 7-30% for shipping cost to the listed FOB² prices. In addition, import duties exist in some countries and the cost of distribution inside the country should also be considered to obtain the real cost of antituberculosis drugs delivered to the patients, even when they are given free of charge to patients.

¹ cost, insurance, freight.

² free-on-board.

Before making the purchase order, it is essential to ensure that the financial resources for purchase (often in hard currencies) are available, and to consider production and delivery delays and other financial resources for distribution and storage inside the country.

9.8 Distributing and storing antituberculosis drugs

Special consideration should be given to the distribution and storage of antituberculosis drugs (as of other essential drugs) at intermediate and peripheral level. Drug stocks should be distributed from national to intermediate level on a regular quarterly basis, rather than yearly, to ensure even distribution. The following factors are all of crucial importance: storage conditions (temperature and humidity); management inside the stores (appropriate space for stocks, control of expiry date, implementation of FIFO principle, reserve stocks); conditions of handling and transportation to district level; implementation of a drug accounting system at all levels where the drugs are stored or administered.

9.9 Rational use of antituberculosis drugs

The provision of adequate information about antituberculosis drugs to the prescribers and the public is essential for their rational and safe use. Independent, reliable and objective information for prescribers can be provided in a number of ways, which should be applied together:

- by a national drug information bulletin or newsletter;
- by national formularies;
- through training programmes and continuing medical, nursing and pharmacy education symposia;
- by formulation of guidelines on standardized treatments.

For patients, many ways can be used to improve drug use and compliance: proper labelling, posters, blister packs, and patient education provided individually and in groups within the existing health services. During supervisory visits to treatment facilities, NTP staff can assess locally how antituberculosis drugs are administered. Rational use by patients is enhanced by direct observation of drug ingestion; it can also be enhanced by efforts to ensure that drugs are not diverted for private sale. The use of reserve antituberculosis drugs should be strictly prohibited and limited for use by specialized units.

9.10 Role of the national drug regulatory authority

In the context of a national drug policy, a drug regulatory authority or similar body can help the rational supply and use of antituberculosis drugs through several mechanisms:

- registration and approval of drugs entering the national market;
- quality control, including bioavailability studies of essential drugs (and fixed-dose combinations of drugs) by a laboratory independent from the producers and the suppliers;
- packaging and labelling of drugs;
- inspection of sites of drug production and of storage;
- quality control during the distribution from central to the most peripheral level;
- monitoring of side-effects;
- monitoring of drug resistance.

9.11 Conclusion

The supply and use of antituberculosis drugs do not occur in a vacuum. Nearly all countries have a general national drug supply system. When feasible, antituberculosis drug supply and training of staff should be integrated into the essential drugs programme and into the national system (e.g. procedures for tender bids, storage and distribution, drug quality control). This should lead to increased efficiency and long-term sustainability.

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10 HIV INFECTION AND TUBERCULOSIS

10.1 Objectives of chapter

This chapter briefly describes:

- HIV-related TB (TB/HIV) as part of the overall TB epidemic
- HIV-related TB as part of the overall HIV/AIDS epidemic
- patterns of HIV-related TB and the effect of HIV on diagnosis
- the implications of HIV for treatment of TB in HIV-infected patients
- the implications of HIV for TB control programmes
- HIV voluntary counselling and testing
- TB treatment and antiretroviral therapy
- collaboration between TB and HIV/AIDS programmes.

10.2 HIV-related TB as part of the overall TB epidemic

Untreated HIV infection leads to progressive immunodeficiency and increased susceptibility to infections, including TB. HIV fuels the TB epidemic by promoting progression of recent and latent *M. tuberculosis* infection to active TB disease. HIV also increases the rate of recurrent TB. Increasing numbers of TB cases in people living with HIV/AIDS pose an increased risk of TB transmission to the general community. Although only a small fraction of the two billion persons infected with TB also have HIV (TB/HIV coinfection), this small group is at high risk of developing TB disease. TB disease probably occurs in half of all people coinfecting with TB and HIV.

10.3 HIV-related TB as part of the overall HIV/AIDS epidemic

The overwhelming share of the global HIV burden is borne by developing countries, where 95% of HIV-infected people live. Of the global total of 36.1 million people living with HIV/AIDS at the end of 2000, 25.3 million (70.1%) were in sub-Saharan Africa and 5.8 million (16.1%) were in South-East Asia. Tuberculosis is a leading cause of morbidity and mortality in populations with high HIV prevalence.

An estimated one-third of the 36.1 million people living with HIV/AIDS worldwide at the end of 2000 were coinfecting with *M. tuberculosis*. Since 68% of those coinfecting live in sub-Saharan Africa, this region also carries the overwhelming burden of the global epidemic of HIV-associated TB. However,

with 22% of those coinfecting and a larger total population, South-East Asia also bears a considerable and growing burden of HIV-associated TB.

10.4 Patterns of HIV-related TB and effect of HIV on diagnosis

As HIV infection progresses, CD4 lymphocytes decline in number and function. The immune system is less able to prevent the growth and local spread of *M. tuberculosis*. Disseminated and extrapulmonary disease is more common.

10.4.1 Adult pulmonary TB

Even in HIV-infected patients, pulmonary TB is still the commonest form of TB. The presentation depends on the degree of immunosuppression. Table 10.1 shows how the clinical picture, sputum smear result and chest X-ray appearance often differ in early and late HIV infection.

Table 10.1 How pulmonary TB differs in early and late HIV infection

FEATURES OF PULMONARY TB	STAGE OF HIV INFECTION	
	EARLY	LATE
Clinical picture	Often resembles post-primary PTB	Often resembles primary PTB
Sputum smear result	Often positive	Often negative
Chest X-ray appearance	Often cavities (may be normal)	Often infiltrates with no cavities (may be normal)

Reported case rates of smear-negative pulmonary TB have increased in association with the TB/HIV co-epidemic. There is a lack of a widely available “gold standard” diagnostic test for smear-negative pulmonary TB. It is often difficult to distinguish other HIV-related pulmonary diseases from pulmonary TB. The extent of over-diagnosis of smear-negative pulmonary TB is therefore uncertain. It is important to follow recommended diagnostic guidelines as closely as possible **and to ensure good quality control of sputum smear microscopy** in order to diagnose smear-negative pulmonary TB as accurately as possible.

10.4.2 Adult extrapulmonary TB

The commonest forms of adult EPTB are pleural effusion, lymphadenopathy, pericardial and meningeal disease, and haematogenous (disseminated)/miliary.

10.4.3 *Childhood TB*

The most frequent presentation of childhood TB is extrapulmonary TB (most commonly intrathoracic). Pulmonary TB is usually smear-negative. As in adults, the natural history of TB in a child infected with HIV depends on the stage of HIV disease. Early in HIV infection, when immunity is good, the signs of TB are similar to those in a child without HIV infection. As HIV infection progresses and immunity declines, dissemination of TB becomes more common. Tuberculous meningitis, miliary TB, and widespread tuberculous lymphadenopathy occur. The current diagnostic approach to childhood TB is even more limited in HIV-infected patients. In the absence of improved diagnostic methods, the diagnosis of childhood TB still rests largely on careful clinical assessment and growth monitoring, chest X-ray, tuberculin test and a positive family history of TB.

10.5 *Implications of HIV for treatment of TB in HIV-infected patients*

10.5.1 *TB treatment in HIV-infected TB patients*

The same criteria determine diagnostic categories for TB patients irrespective of HIV status. Thus, HIV-infected new TB patients receive Category I treatment if they have smear-positive pulmonary TB, smear-negative pulmonary TB with extensive parenchymal involvement, or severe forms of extrapulmonary TB.

Generally, TB treatment is the same for HIV-infected as for non-HIV-infected TB patients, with the exception of the use of thioacetazone. Streptomycin remains a useful drug in countries that can ensure the use of disposable or sterile needles and syringes.

10.5.2 *Adverse drug reactions*

HIV infection is associated with an increased risk of adverse drug reactions to many antituberculosis drugs. Thioacetazone is associated with a high risk of severe, and sometimes fatal, skin reaction in HIV-infected individuals. Ethambutol should therefore be used instead of thioacetazone in patients with known or suspected HIV infection, and used in general instead of thioacetazone in regions or countries where the level of HIV infection is known to be high.

10.5.3 *Response of HIV-infected TB patients to TB treatment*

Clinical course during TB treatment

Common HIV-related infections (e.g. pneumonia and diarrhoea and their complications, fungal infections) cause considerable morbidity during treatment of HIV-infected TB patients, and contribute to the increased case fatality. Patients should be monitored during TB treatment to identify and treat these infections.

Case fatality

HIV-infected smear-positive TB patients have an increased case fatality. In HIV-infected smear-negative TB patients, the case fatality is even higher, probably reflecting their greater degree of immunosuppression. Excess deaths in HIV-infected TB patients during and after treatment are partly due to TB itself and partly due to other HIV-related problems.

Co-trimoxazole prophylaxis

Prophylaxis against intercurrent infections may decrease morbidity and mortality in HIV-infected tuberculosis patients. The Joint United Nations Programme on HIV/AIDS (UNAIDS) and WHO have provisionally recommended the use of co-trimoxazole prophylaxis in HIV-infected individuals in Africa as part of a minimum package of care. The recommended dose of co-trimoxazole (sulfamethoxazole (SMX) and trimethoprim (TMP) 5:1) for adults is 960 mg once daily, and for children SMX 20 mg/kg, TMP 4 mg/kg once daily. Further studies are needed to evaluate the benefits and duration of treatment, and the feasibility and effectiveness of this intervention under routine conditions.

Response in survivors

Several studies have assessed the clinical, radiological, and microbiological response to 6 months' rifampicin-based treatment in HIV-positive and HIV-negative TB patients. Excluding patients who died, response rates were similar in HIV-positive and HIV-negative TB patients. There is little information about the efficacy of 8-month regimens in TB/HIV. However, regimens that do not contain rifampicin in the continuation phase have been associated with a greater risk of failure or relapse compared with 6-month regimens with rifampicin.

Recurrence of TB after completion of TB treatment

Among TB patients who complete short-course chemotherapy, the recurrence rate is higher in HIV-positive than in HIV-negative TB patients. Post-treatment prophylaxis (for example with isoniazid) can decrease the risk of TB recurrence in HIV-infected individuals, although it does not appear to prolong survival. Further studies are needed to confirm the benefit, establish the optimum regimen (drugs and duration) and assess the operational feasibility, before treatment aimed at decreasing the risk of TB recurrence is widely recommended.

10.6 Implications of HIV for TB control programmes**10.6.1 Difficulties with targets for cure rates and case detection**

High death rates and high rates of adverse drug reactions giving rise to increased default rates are preventing many countries with high HIV prevalence from meeting the global cure rate target of 85%. National TB programmes need to interpret the cure rate as an indicator of NTP performance, taking into consideration the increased death rates associated with high HIV prevalence.

10.6.2 *Need for more resources for TB control*

Increased TB case numbers as a result of the HIV epidemic have meant a need for increased investment to improve general health service capacity to deliver TB control interventions (human resources, infrastructure and commodities, e.g. laboratory resources, drugs, sputum containers and stationery).

10.6.3 *Need for decentralization because of overcrowded TB wards*

Large numbers of patients have led to overcrowding of TB wards, making good nursing care difficult and increasing the risk of nosocomial infection. One response of NTPs is to decentralize treatment to peripheral health centres and the community. This patient-friendly approach requires strong managerial capacity to ensure the logistics of directly observed treatment, drug security (especially of rifampicin), supervision, monitoring and recording in the community.

10.6.4 *Need to reduce risk of nosocomial TB transmission*

Health care staff in outpatient and inpatient facilities, where HIV prevalence is similar to that in the general population, are at risk of nosocomially acquired TB. HIV-infected patients in the same health facilities as TB suspects may also be at increased risk of TB. Measures are therefore necessary to protect health care staff and patients from nosocomial TB transmission.

10.7 *HIV voluntary counselling and testing of individual TB patients*

In countries where the link between HIV and TB is well known to many members of the public, TB patients may be well aware of the possibility of also having HIV infection. It is important to offer counselling and, if available, voluntary HIV testing to TB patients for the following reasons:

- the opportunity for patients to know their HIV status and prognosis;
- better diagnosis and management of other HIV-related illnesses;
- avoidance of drugs associated with a high risk of side-effects;
- increased condom use and decreased HIV transmission;
- opportunities for prevention of other infections (e.g. using co-trimoxazole)
- opportunities for antiretroviral therapy, if available.

A policy of compulsory HIV testing of TB patients would be counterproductive (even if it were legal). This type of policy would deter patients from seeking care, reduce case-finding in at-risk groups and lower the credibility of health services.

Counselling with the assurance of confidentiality is essential before and after HIV antibody testing. The patient gives explicit informed consent for the test, i.e. the patient understands what the test involves and the implications of testing. Counselling is a dialogue between the patient and the counsellor, who provides information and support.

10.8 TB treatment and antiretroviral therapy

Highly active antiretroviral therapy (HAART) is not a cure for HIV infection but is associated with dramatic reductions in morbidity and mortality in HIV-infected people. Although HAART is now the standard of care in the industrialized world, very few HIV-infected people currently have access to HAART where the burden of HIV is greatest (in sub-Saharan Africa and Asia). International pressure is mounting to ensure that more people in countries with high HIV prevalence have access to these drugs. There are several requirements for successful treatment of HIV infection with HAART. These include considerable efforts to maintain adherence to lifelong treatment and to monitor response to treatment, drug toxicities and drug interactions.

Currently available antiretroviral drugs belong to two major classes:

- reverse transcriptase inhibitors (RTIs), which may be nucleoside (NRTIs) or non nucleoside (NNRTIs);
- protease inhibitors (PIs).

Examples of some of these drugs are given below:

NRTIs zidovudine (AZT, ZDV), didanosine (ddI), zalcitabine (ddC),
 stavudine (d4T), lamivudine (3TC), abacavir (ABC)

NNRTIs nevirapine (NVP), efavirenz (EFV), delavirdine (DLV)

PIs saquinavir (SQV), ritonavir (RTV), indinavir (IDV), nelfinavir (NFV),
 amprenavir (APV), lopinavir/ritonavir.

These drugs act by blocking the action of enzymes important for the replication and functioning of HIV. The drugs must be used in combination, usually 3 drugs together. Monotherapy is not recommended because of the inevitable development of drug resistance. However, for the specific indication of prevention of mother-to-child transmission of HIV infection, short-course monotherapy is recommended. Dual nucleoside therapy is also not recommended because it has no beneficial impact at a population level in terms of reducing HIV-related mortality.

The WHO document *Safe and effective use of antiretroviral treatments in adults, with particular reference to resource limited settings*¹ provides information about antiretroviral drugs and HAART regimens. The following section provides a brief summary of information relevant to the treatment of HIV-infected TB patients with antiretroviral drugs.

¹ *Safe and effective use of antiretroviral treatments in adults, with particular reference to resource limited settings*. Geneva, World Health Organization, 2000 (document WHO/HSI/2000.04).

10.8.1 *Drug interactions*

Rifampicin stimulates the activity of the cytochrome P450 liver enzyme system that metabolizes PIs and NNRTIs. This can lead to a reduction in the blood levels of PIs and NNRTIs. Protease inhibitors and NNRTIs can also enhance or inhibit this same enzyme system, and lead to altered blood levels of rifampicin. The potential drug interactions may result in ineffectiveness of antiretroviral drugs, ineffective treatment of TB, and an increased risk of drug toxicity.

Occasionally, patients with HIV-related TB may experience a temporary exacerbation of symptoms, signs or radiographic manifestations of TB after beginning TB treatment. This paradoxical reaction occurs in HIV-infected patients with active TB and is thought to be a result of immune restitution due to the simultaneous administration of antiretroviral and tuberculosis medications. Symptoms and signs may include high fever, lymphadenopathy, expanding central nervous system lesions and worsening of chest radiographic findings. The diagnosis of a paradoxical reaction should be made only after a thorough evaluation has excluded other etiologies, particularly TB treatment failure. For severe paradoxical reactions prednisone (1-2 mg/kg for 1-2 weeks, then gradually decreasing doses) may be used, although there are no data to support this approach.

Isoniazid can produce peripheral neuropathy. The NRTIs (didanosine, zalcitabine and stavudine) may also produce peripheral neuropathy and there is a potential further toxicity if isoniazid is added. Isoniazid also has a theoretical interaction with abacavir.

10.8.2 *Treating TB and HIV together*

In patients with HIV-related TB, the priority is to treat TB, especially smear-positive PTB cases. However, with careful management, patients with HIV-related TB can have antiretroviral therapy at the same time as TB treatment.

Possible options for antiretroviral therapy in TB patients include:

- defer antiretroviral therapy until TB treatment is completed
- defer antiretroviral therapy until the end of the initial phase of treatment and use ethambutol and isoniazid in the continuation phase
- treat TB with a rifampicin-containing regimen and use efavirenz + 2 NRTIs
- treat TB with a rifampicin-containing regimen and use 2 NRTIs; then change to a maximally suppressive HAART regimen on completion of TB treatment.

10.9 Collaboration between TB and HIV/AIDS programmes

10.9.1 *Areas of mutual concern of TB and HIV/AIDS programmes*

Since HIV fuels the TB epidemic, HIV programmes and TB programmes share mutual concerns: prevention of HIV should be a priority for TB control; TB care and prevention should be priority concerns for HIV/AIDS programmes.

10.9.2 *The expanded scope of a new approach for TB control in high HIV prevalence populations*

So far, efforts to control TB among HIV-infected people have focused mainly on implementing the DOTS strategy for TB control, i.e. identifying and curing infectious TB cases. This targets the final step in the sequence of events by which HIV fuels TB, namely the transmission of *M. tuberculosis* infection by infectious TB cases. The expanded scope of a new approach to TB control in populations with high HIV prevalence comprises interventions against TB (intensified case-finding and cure and TB preventive therapy) and interventions against HIV (and therefore indirectly against TB), e.g. condoms, treatment of sexually transmitted infections or prophylaxis and HAART. Whereas previously TB programmes and HIV/AIDS programmes have largely pursued separate courses, they now need to collaborate in areas of mutual concern in their support to general health service providers.

10.9.3 *Coordinated care of HIV-infected TB patients*

National TB programme staff and general health service staff should be aware that many HIV-positive TB patients develop other HIV-related illnesses during TB treatment. Delivering interventions to reduce the frequency of opportunistic infections (e.g. co-trimoxazole prophylaxis, antiretroviral therapy) requires effective collaboration with HIV/AIDS programmes. Continuity of care for HIV-infected TB patients requires coordination of care in different settings and at different levels. Sometimes patients know that they are HIV-positive and later on develop TB. More often, patients find out that they are HIV-positive only after developing TB. In either case, the TB control programme needs to coordinate closely with other services providing support and care for HIV-positive individuals. The clinician who treats the HIV-infected TB patient is in a key position to refer the patient to appropriate services for counselling, support, and care of the patient and their family.

Suggestions for further reading

Guidelines for the prevention of tuberculosis in health care facilities in resource-limited settings. Geneva, World Health Organization, 1999 (document WHO/CDS/TB/99.269).

Harries AD, Maher D. TB/HIV: a clinical manual. Geneva, World Health Organization, 1996 (document WHO/TB/96.200).

Maher D, Floyd K, Raviglion MC. Strategic framework to decrease the burden of TB/HIV. Geneva, World Health Organization, 2002 (document WHO/CDS/TB/2002.296).

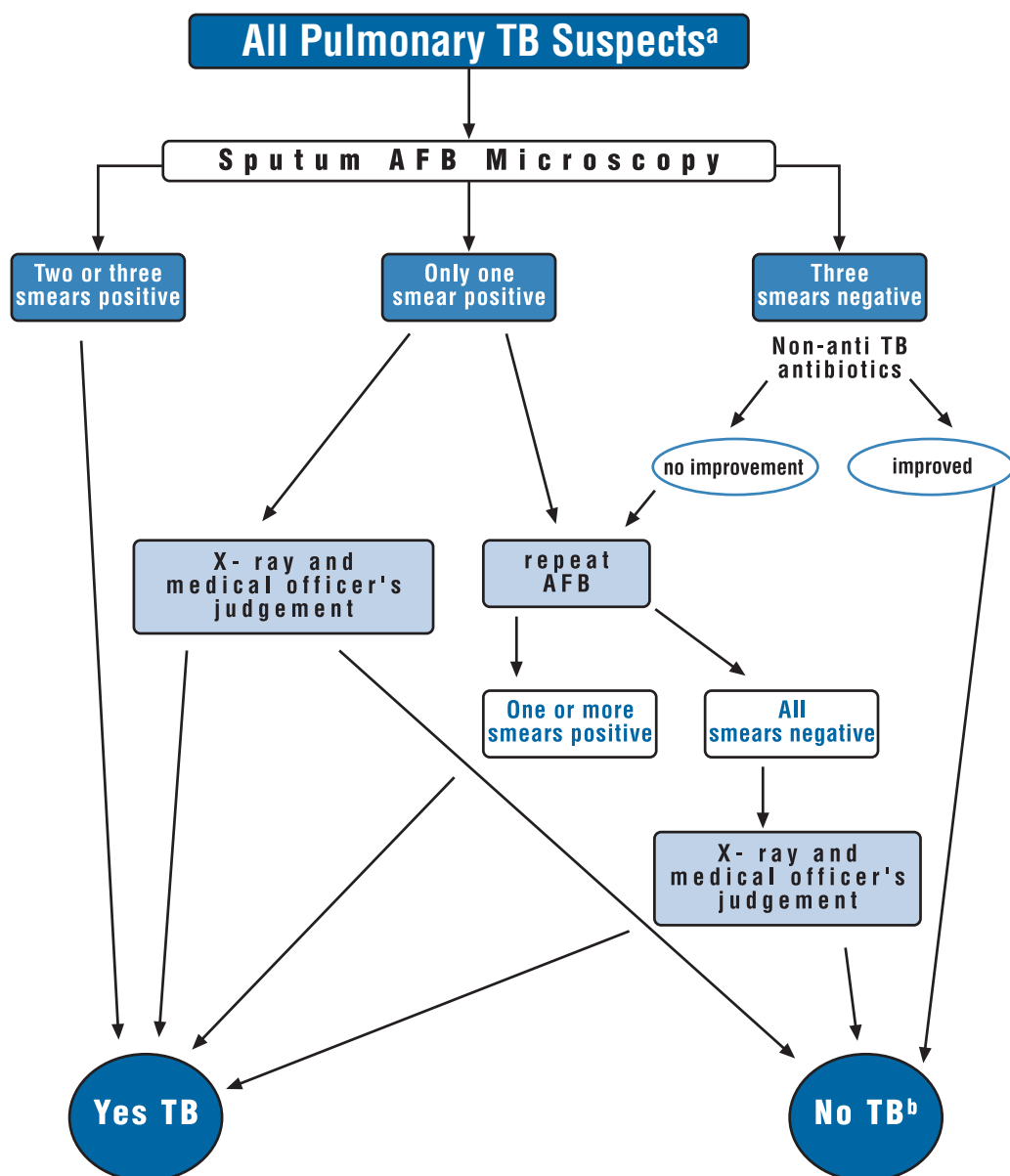
Preventive therapy against tuberculosis in people living with HIV. Weekly Epidemiological Record, 1999, 74:385-398.

*Provisional WHO/UNAIDS Secretariat recommendations on the use of cotrimoxazole prophylaxis in adults and children living with HIV/AIDS in Africa. Geneva, Joint United Nations Programme on HIV/AIDS, 2000
(<http://www.unaids.org/publications/documents/care/general/recommendation-eng.pdf>).*



ANNEX 1

DIAGNOSTIC PROCEDURE FOR SUSPECTED PULMONARY TB

^a Screening: cough >2-3 weeks. Diagnosis: clinical signs, symptoms, normal chest radiography.^b Consider other diagnoses.



ESSENTIAL ANTITUBERCULOSIS DRUGS

ISONIAZID

Group: antimycobacterial agent

Tablet: 100 mg, 300 mg

Injection (solution for injection): 25 mg/ml in 2-ml ampoule

General information

Isoniazid, the hydrazide of isonicotinic acid, is highly bactericidal against replicating tubercle bacilli.

It is rapidly absorbed and diffuses readily into all fluids and tissues. The plasma half-life, which is genetically determined, varies from less than 1 hour in fast acetylators to more than 3 hours in slow acetylators. It is largely excreted in the urine within 24 hours, mostly as inactive metabolites.

Clinical information

USES

A component of all TB chemotherapeutic regimens currently recommended by WHO.

Isoniazid alone is occasionally used to prevent:

- transmission to close contacts at high risk of disease;
- progression of infection to primary complex in recently infected, asymptomatic individuals;
- development of active TB in immunodeficient individuals.

ADMINISTRATION AND DOSAGE

Isoniazid is normally taken orally but may be administered intramuscularly to critically ill patients.

TREATMENT (COMBINATION THERAPY)

Adults and children: 5 mg/kg (4-6 mg/kg) daily, maximum 300 mg
 10 mg/kg 3 times weekly
 15 mg/kg 2 times weekly

PREVENTIVE THERAPY

Adults: 300 mg/kg daily for at least 6 months
 Children: 5 mg/kg daily (maximum 300 mg) for at least 6 months

CONTRAINDICATIONS

- Known hypersensitivity.
- Active hepatic disease.

PRECAUTIONS

Monitoring of serum concentrations of hepatic transaminases, where possible, is useful in patients with pre-existing chronic liver disease. Patients at risk of peripheral neuropathy, as a result of malnutrition, chronic alcohol dependence or diabetes, should additionally receive pyridoxine, 10 mg daily. Where the standard of health in the community is low, this should be offered routinely.

Since isoniazid interacts with anticonvulsants used for epilepsy, it may be necessary to reduce the dosage of these drugs during treatment with isoniazid.

USE IN PREGNANCY

Whenever possible, the 6-month regimen based upon isoniazid, rifampicin and pyrazinamide should be used.

ADVERSE EFFECTS

Isoniazid is generally well tolerated at recommended doses. Systemic or cutaneous hypersensitivity reactions occasionally occur during the first weeks of treatment.

The risk of peripheral neuropathy is excluded if vulnerable patients receive daily supplements of pyridoxine. Other less common forms of neurological disturbance, including optic neuritis, toxic psychosis and generalized convulsions, can develop in susceptible individuals, particularly in the later stages of treatment, which occasionally necessitate the withdrawal of isoniazid.

Hepatitis is an uncommon but potentially serious reaction that can usually be averted by prompt withdrawal of treatment. More often, however, a sharp rise in serum concentrations of hepatic transaminases at the outset of treatment is not of clinical significance, and usually resolves spontaneously during continuation of treatment.

DRUG INTERACTIONS

Isoniazid tends to raise plasma concentrations of phenytoin and carbamazepine by inhibiting their metabolism in the liver. The absorption of isoniazid is impaired by aluminium hydroxide.

OVERDOSAGE

Nausea, vomiting, dizziness, blurred vision and slurring of speech occur within 30 minutes to 3 hours of overdosage. Massive poisoning results in coma preceded by respiratory depression and stupor. Severe intractable seizures may occur. Emesis

and gastric lavage, activated charcoal, antiepileptics and IV sodium bicarbonate can be of value if instituted within a few hours of ingestion. Subsequently, haemodialysis may be of value. Administration of high doses of pyridoxine is necessary to prevent seizures.

STORAGE

Tablets should be kept in well-closed containers, protected from light. Solution of injection should be stored in ampoules, protected from light.

RIFAMPICIN

Group: antimycobacterial agent

Capsule or tablet: 150 mg, 300 mg

General information

A semisynthetic derivative of rifamycin, a complex macrocyclic antibiotic that inhibits ribonucleic acid synthesis in a broad range of microbial pathogens. It has bactericidal action and a potent sterilizing effect against tubercle bacilli in both cellular and extracellular locations.

Rifampicin is lipid-soluble. Following oral administration, it is rapidly absorbed and distributed throughout the cellular tissues and body fluids; if the meninges are inflamed, significant amounts enter the cerebrospinal fluid. A single dose of 600 mg produces a peak serum concentration of about 10 µg/ml in 2-4 hours, which subsequently decays with a half-life of 2-3 hours. It is extensively recycled in the enterohepatic circulation, and metabolites formed by deacetylation in the liver are eventually excreted in the faeces.

Since resistance readily develops, rifampicin must always be administered in combination with other effective antimycobacterial agents.

Clinical information

USES

A component of all 6- and 8-month TB chemotherapeutic regimens currently recommended by WHO (see Table 4.3).

ADMINISTRATION AND DOSAGE

Rifampicin should preferably be given at least 30 minutes before meals, since absorption is reduced when it is taken with food. This may not, however, be clinically significant, and food can reduce intolerance to drugs.

Adults and children: 10 mg/kg (8-12 mg/kg) daily, maximum 600 mg daily,
2 or 3 times weekly

CONTRAINDICATIONS

- Known hypersensitivity to rifamycins.
- Hepatic dysfunction.

PRECAUTIONS

Serious immunological reactions resulting in renal impairment, haemolysis or thrombocytopenia are on record in patients who resume taking rifampicin after a prolonged lapse of treatment. In this rare situation, it should be immediately and definitely withdrawn.

Careful monitoring of liver function is required in the elderly and in patients who are alcohol-dependent or have hepatic disease.

Patients should be warned that treatment may produce reddish coloration of urine, tears, saliva and sputum, and that contact lenses may be irreversibly stained.

USE IN PREGNANCY

Whenever possible, the 6-month regimen based upon isoniazid, rifampicin and pyrazinamide should be used.

Vitamin K should be administered at birth to the infant of a mother taking rifampicin because of the risk of postnatal haemorrhage.

ADVERSE EFFECTS

Rifampicin is well tolerated by most patients at currently recommended doses, although gastrointestinal intolerance can be unacceptably severe. Other adverse effects (fever, influenza-like syndrome and thrombocytopenia) are more likely to occur with intermittent administration, and skin rashes just as likely. Exfoliative dermatitis is more frequent in HIV-positive TB patients. Temporary oliguria, dyspnoea and haemolytic anaemia have also been reported in patients taking the drug 3 times weekly. These reactions usually subside if the regimen is changed to one with daily dosage.

Moderate rises in serum concentrations of bilirubin and transaminases, which are common at the outset of treatment, are often transient and without clinical significance. However, dose-related hepatitis can occur, which is potentially fatal. It is consequently important not to exceed the maximum recommended daily dose of 10 mg/kg (600 mg).

DRUG INTERACTIONS

Rifampicin induces hepatic enzymes, and may increase the dosage requirements of drugs metabolized in the liver. These include corticosteroids, steroid contraceptives, oral hypoglycaemic agents, oral anticoagulants, phenytoin, cimetidine, cyclosporin and digitalis glycosides. Since rifampicin reduces the effectiveness of oral contraceptives, women should be advised to choose between

one of the following two options for contraception. Following consultation with a clinician, the patient may use an oral contraceptive pill containing a higher dose of estrogen (50 µg). Alternatively, a nonhormonal method of contraception may be used throughout rifampicin treatment and for at least one month subsequently.

Current antiretroviral drugs (NNRTIs and PIs) interact with rifampicin. This may result in ineffectiveness of antiretroviral drugs, ineffective treatment of TB or an increased risk of drug toxicity.

Biliary excretion of radiocontrast media and sulfobromophthalein sodium may be reduced and microbiological assays for folic acid and vitamin B₁₂ disturbed.

OVERDOSAGE

Gastric lavage may be of value if undertaken within a few hours of ingestion. Very large doses may depress central nervous function. There is no specific antidote and treatment is supportive.

STORAGE

Capsules and tablets should be kept in tightly closed containers, protected from light.

ISONIAZID/RIFAMPICIN

General information

A fixed-dose combination of rifampicin and isoniazid intended to promote compliance. It is essential that all such products be shown to have adequate bioavailability.

Clinical information

USES

Both drugs are components of all 6- and 8-month TB chemotherapeutic regimens currently recommended by WHO.

DOSAGE

There are different dosage forms, for daily use and for intermittent use, in adults and children.

For daily use: tablets of 150 mg isoniazid + 300 mg rifampicin
tablets of 75 mg isoniazid + 150 mg rifampicin
tablet or pack of granules for paediatric use:
30 mg isoniazid + 60 mg rifampicin.

For intermittent use (3 times weekly):
tablets of 150 mg isoniazid + 150 mg rifampicin
tablet or pack of granules for paediatric use:
60 mg isoniazid + 60 mg rifampicin.

PYRAZINAMIDE

Group: antimycobacterial agent

Tablet: 400 mg

General information

A synthetic analogue of nicotinamide that is only weakly bactericidal against *M. tuberculosis* but has potent sterilizing activity, particularly in the relatively acidic intracellular environment of macrophages and in areas of acute inflammation. It is highly effective during the first 2 months of treatment while acute inflammatory changes persist and its use has enabled treatment regimens to be shortened and the risk of relapse to be reduced.

It is readily absorbed from the gastrointestinal tract and is rapidly distributed throughout all tissues and fluids. Peak plasma concentrations are attained in 2 hours and the plasma half-life is about 10 hours. It is metabolized mainly in the liver and is excreted largely in the urine.

*Clinical information***USES**

A component of all 6- and 8-month TB chemotherapeutic regimens currently recommended by WHO.

DOSAGE

Adults and children (for the first 2 or 3 months):
25 mg/kg daily (20-30 mg/kg),
35 mg/kg (30-40 mg/kg) 3 times weekly,
50 mg/kg (40-60 mg/kg) 2 times weekly.

CONTRAINDICATIONS

- Known hypersensitivity.
- Severe hepatic impairment.

PRECAUTIONS

Patients with diabetes should be carefully monitored since blood glucose concentrations may become labile. Gout may be exacerbated.

USE IN PREGNANCY

The 6-month regimen based upon isoniazid, rifampicin and pyrazinamide should be used whenever possible.

ADVERSE EFFECTS

Pyrazinamide may cause gastrointestinal intolerance. Hypersensitivity reactions are rare, but some patients complain of slight flushing of the skin.

Moderate rises in serum transaminase concentrations are common during the early phases of treatment. Severe hepatotoxicity is rare.

As a result of inhibition of renal tubular secretion, a degree of hyperuricaemia usually occurs, but this is often asymptomatic. Gout requiring treatment with allopurinol occasionally develops. Arthralgia, particularly of the shoulders, may occur and is responsive to simple analgesics (especially aspirin). Both hyperuricaemia and arthralgia may be reduced by prescribing regimens with intermittent administration of pyrazinamide.

OVERDOSAGE

Little has been recorded on the management of pyrazinamide overdose. Acute liver damage and hyperuricaemia have been reported. Treatment is essentially symptomatic. Emesis and gastric lavage may be of value if undertaken within a few hours of ingestion. There is no specific antidote and treatment is supportive.

STORAGE

Tablets should be stored in tightly closed containers, protected from light.

STREPTOMYCIN

Group: antimycobacterial agent

Injection (powder for solution for injection): 1 g (as sulfate) in vial

General information

An aminoglycoside antibiotic derived from *Streptomyces griseus* that is used in the treatment of TB and sensitive Gram-negative infections.

Streptomycin is not absorbed from the gastrointestinal tract but, after intramuscular administration, it diffuses readily into the extracellular component of most body tissues and attains bactericidal concentrations, particularly in tuberculous cavities. Little normally enters the cerebrospinal fluid, although penetration increases when the meninges are inflamed. The plasma half-life, which is normally 2-3 hours, is considerably extended in the newborn, the elderly, and patients with severe renal impairment. It is excreted unchanged in the urine.

Clinical information

USES

A component of several TB chemotherapeutic regimens currently recommended by WHO.

ADMINISTRATION AND DOSAGE

Streptomycin must be administered by deep intramuscular injection. Syringes and needles should be adequately sterilized to exclude any risk of transmitting viral pathogens.

Adults and children: 15 mg/kg (12-18 mg/kg) daily, or 2 or 3 times weekly.

Patients aged over 60 years may not be able to tolerate more than 500-750 mg daily.

CONTRAINDICATIONS

- Known hypersensitivity.
- Auditory nerve impairment.
- Myasthenia gravis.

PRECAUTIONS

Hypersensitivity reactions are rare. If they do occur (usually during the first weeks of treatment), streptomycin should be withdrawn immediately. Once fever and skin rash have resolved, desensitization may be attempted.

Streptomycin should be avoided in children, when possible, because the injections are painful and irreversible auditory nerve damage may occur. Both the elderly and patients with renal impairment are also vulnerable to dose-related toxic effects resulting from accumulation. Where facilities are available to monitor renal function closely, it may be possible to give streptomycin in reduced doses to patients with renal impairment. Where possible, serum levels should be monitored periodically and dosage adjusted appropriately to ensure that plasma concentrations, measured when the next dose is due, do not rise above 4 µg/ml.

Protective gloves should be worn when streptomycin injections are administered, to avoid sensitization dermatitis.

USE IN PREGNANCY

Streptomycin should not be used in pregnancy. It crosses the placenta and can cause auditory nerve impairment and nephrotoxicity in the fetus.

ADVERSE EFFECTS

Injections are painful and sterile abscesses can form at injection sites. Hypersensitivity reactions are common and can be severe.

Impairment of vestibular function is uncommon with currently recommended doses. Dosage should be reduced if headache, vomiting, vertigo and tinnitus occur.

Streptomycin is less nephrotoxic than other aminoglycoside antibiotics. Dosage must be reduced by half immediately if urinary output falls, if albuminuria occurs or if tubular casts are detected in the urine.

Haemolytic anaemia, aplastic anaemia, agranulocytosis, thrombocytopenia and lupoid reactions are rare adverse effects.

DRUG INTERACTIONS

Other ototoxic or nephrotoxic drugs should not be administered to patients receiving streptomycin. These include other aminoglycoside antibiotics, amphotericin B, cephalosporins, etacrynic acid, cyclosporin, cisplatin, furosemide and vancomycin.

Streptomycin may potentiate the effect of neuromuscular blocking agents administered during anaesthesia.

OVERDOSAGE

Haemodialysis can be beneficial. There is no specific antidote and treatment is supportive.

STORAGE

Solutions retain their potency for 48 hours after reconstitution at room temperature and for up to 14 days when refrigerated. Powder for injection should be stored in tightly closed containers, protected from light.

ETHAMBUTOL

Group: antimycobacterial agent

Tablet: 100 mg, 400 mg (hydrochloride)

General information

A synthetic congener of 1,2-ethanediamine that is active against *M. tuberculosis*, *M. bovis* and some nonspecific mycobacteria. It is used in combination with other antituberculosis drugs to prevent or delay the emergence of resistant strains.

It is readily absorbed from the gastrointestinal tract. Plasma concentrations peak in 2-4 hours and decay with a half-life of 3-4 hours. Ethambutol is excreted in the urine both unchanged and as inactive hepatic metabolites.

About 20% is excreted in the faeces as unchanged drug.

Clinical information

USES

An optional component of several TB chemotherapeutic regimens currently recommended by WHO.

DOSAGE

Adults: 15 mg/kg (15-20 mg/kg) daily
 30 mg/kg (25-35 mg/kg) 3 times weekly, or
 45 mg/kg (40-50 mg/kg) 2 times weekly.

Children: maximum 15 mg/kg daily.

Dosage must always be carefully calculated on a weight basis to avoid toxicity, and should be reduced in patients with impaired renal function.

CONTRAINDICATIONS

- Known hypersensitivity.
- Pre-existing optic neuritis from any cause.
- Creatinine clearance of less than 50 ml/minute.

PRECAUTIONS

Patients should be advised to discontinue treatment immediately and to report to a clinician if their sight or perception of colour deteriorates. Whenever possible, renal function should be assessed before treatment.

USE IN PREGNANCY

The 6-month regimen based upon isoniazid, rifampicin and pyrazinamide should be used. Ethambutol should be used if a fourth drug is needed during the initial phase.

ADVERSE EFFECTS

Dose-dependent optic neuritis can result in impairment of visual acuity and colour vision. Early changes are usually reversible, but blindness can occur if treatment is not discontinued promptly. Ocular toxicity is rare when used for 2-3 months at recommended doses.

Signs of peripheral neuritis occasionally develop in the legs.

OVERDOSAGE

Emesis and gastric lavage may be of value if undertaken within a few hours of ingestion. Subsequently, dialysis may be of value. There is no specific antidote and treatment is supportive.

STORAGE

Tablets should be stored in well-closed containers.

ISONIAZID/THIOACETAZONE

General information

A fixed-dose combination of isoniazid and thioacetazone that is almost as inexpensive as isoniazid alone and is intended to promote compliance (single daily pill) and to prevent emergence of isoniazid-resistant bacilli. Thioacetazone, a thiosemicarbazone that is bacteriostatic against *M. tuberculosis*, is used in TB

chemotherapy to inhibit the emergence of resistance to isoniazid, particularly in the continuation phase of the long-term regimens. It is well absorbed from the gastrointestinal tract. Peak concentrations in plasma are attained after 4-6 hours and the plasma half-life is about 12 hours. About one-third of the oral dose is excreted in the urine unchanged. (General information on isoniazid is provided above).

Clinical information

USES

A component of some of the longer TB chemotherapeutic regimens.

DOSAGE

Adults: 300 mg isoniazid + 150 mg thioacetazone daily.
Children: 100 mg isoniazid + 50 mg thioacetazone daily.

CONTRAINDICATIONS

Known hypersensitivity to either component.

PRECAUTIONS

Treatment should be withdrawn immediately if a rash or other signs suggestive of hypersensitivity occur.

ADVERSE EFFECTS

Effects attributable to isoniazid are listed above. The thioacetazone component frequently causes nausea, vomiting, diarrhoea and skin rashes.

Rare cases of fatal exfoliative dermatitis and acute hepatic failure have been reported. Cases of agranulocytosis, thrombocytopenia and aplastic anaemia are also on record. These adverse effects are more frequent in HIV-positive TB patients.

Dose-related ototoxicity is rare, but particularly careful monitoring is required when thioacetazone is used in combination with streptomycin.

OVERDOSAGE

Emesis and gastric lavage may be of value if undertaken within a few hours of ingestion. There is no specific antidote and treatment is supportive.

STORAGE

Tablets should be kept in well-closed containers.

ISONIAZID/ETHAMBUTOL

Group: antimycobacterial agent

Tablet: 150 mg isoniazid + 400 mg ethambutol

General information

A fixed-dose combination of 2 drugs (previously described) intended to promote compliance.

USES

- only for continuation phase;
- always daily (not three times weekly);
- substitutes for isoniazid + thioacetazone combination in patients with side-effects due to thioacetazone, and in areas with high prevalence of HIV infection.

ISONIAZID/RIFAMPICIN/PYRAZINAMIDE

Group: antimycobacterial agent

General information

A fixed-dose combination of 3 drugs (previously described) intended to promote compliance. It is essential that all such products be shown to have adequate bioavailability.

- Daily: tablet 75 mg isoniazid + 150 mg rifampicin + 400 mg pyrazinamide tablet or pack of granules for paediatric use: 30 mg isoniazid + 60 mg rifampicin + 150 mg pyrazinamide.
- 3 times weekly: tablet 150 mg isoniazid + 150 mg rifampicin + 500 mg pyrazinamide.

ISONIAZID/RIFAMPICIN/PYRAZINAMIDE/ETHAMBUTOL

Group: antimycobacterial agent

General information

A fixed-dose combination of 4 drugs (previously described) intended to promote compliance. It is essential that all such products be shown to have adequate bioavailability.

- Daily: tablet 75 mg isoniazid + 150 mg rifampicin + 400 mg pyrazinamide + 275 mg ethambutol.

RESERVE ANTITUBERCULOSIS DRUGS

AMINOGLYCOSIDES

- Kanamycin and amikacin
- Capreomycin (polypeptide)

THIOAMIDES

- Ethionamide
- Protionamide

FLUOROQUINOLONES

- Ofloxacin
- Ciprofloxacin

CYCLOSERINE (AND TERIZIDONE)

P-AMINOSALICYCLIC ACID (PAS)

KANAMYCIN AND AMIKACIN

Kanamycin and amikacin are bactericidal agents of the aminoglycoside class, obtained from *Streptomyces*. Their bactericidal effect in vitro and in vivo against *M. tuberculosis* is very similar and their adverse reactions are those of other aminoglycosides.

Their bactericidal effect may be valuable in patients with bacilli resistant to streptomycin. Cross-resistance between kanamycin and amikacin is usual.

PRESENTATION AND DOSAGE

The drugs are presented as sterile white powder for intramuscular injection in sealed vials containing the equivalent of 250 mg, 500 mg or 1 g of drug. The drug should be dissolved in 2 ml of 0.9% sodium chloride injection or water for injection.

The optimal dose is 15 mg/kg body weight, usually 750 mg to 1 g, given daily or 5 days per week by deep intramuscular injection. Rotation of injection sites avoids local discomfort. The duration of daily therapy is usually 3-4 months. When necessary, the drug may be given at the same dosage 2 or 3 times weekly during the continuation phase, under close monitoring for adverse reactions.

ADVERSE REACTIONS

Side-effects are similar to those associated with streptomycin and capreomycin.

Ototoxicity, deafness, vertigo or reversible nephrotoxicity may occur.

PRECAUTIONS

In patients with impaired renal function, the daily dosage should be reduced and/or the intervals between dosage increased, to avoid accumulation of the drug. In these patients, renal function should be monitored regularly during use. This drug should not be used in pregnant women except as a last resort.

CAPREOMYCIN

Capreomycin is a bactericidal agent from the polypeptide class, obtained from *Streptomyces capreolus*.

Its bactericidal effect may be valuable in patients with bacilli resistant to streptomycin, kanamycin and amikacin; there is no cross-resistance with the other aminoglycosides.

PREPARATION AND DOSAGE

Capreomycin sulfate is supplied as a sterile white powder for intramuscular injection in sealed vials each containing 1000 units, approximately equivalent to 1 g capreomycin base. This should be dissolved in 2 ml of 0.9% sodium chloride; 2-3 minutes should be allowed for complete solution. The usual dosage is 1g in a single daily dose, not exceeding 20 mg/kg, for 40-120 days after which dosage must be reduced to 2 or 3 times weekly, as the risk of important side-effects rises sharply at that time.

ADVERSE REACTIONS

Side-effects are similar to those of streptomycin, mainly tinnitus and vertigo with a lesser risk of deafness. Kidney damage may occur with elevation of serum and urine creatinine. Hypokalaemia, hypocalcaemia and hypomagnesaemia have also been reported. General cutaneous reactions and hepatitis may occur rarely. There may be pain and swelling at injection sites if it is not given by deep intramuscular injection.

PRECAUTIONS

Capreomycin should be avoided, if possible, in patients with impaired hearing or renal function. Serum urea and electrolytes should be monitored during treatment. It is contraindicated in pregnancy and best avoided in children.

ETHIONAMIDE (OR PROTIONAMIDE)

Ethionamide and protionamide are bactericidal agents from the class of thioamides. Their chemical structure resembles thioacetazone with which there is frequent and partial cross-resistance. (Bacilli resistant to thioacetazone are often sensitive to thioamides, but the reverse is seldom the case.)

Before the rifampicin era, ethionamide (or protioanamide - the drug is similar in its antibacterial effects and adverse reactions) was a basic component of re-treatment regimens for tuberculosis patients with bacilli resistant to isoniazid and streptomycin.

ADMINISTRATION AND DOSAGE

Ethionamide and protionamide are normally administered in the form of tablets containing 125 mg or 250 mg of drug. The maximum optimum daily dose is 15-20 mg/kg or 1 g. The usual dose is 500 mg to 1 g daily, depending upon body weight and tolerance. Few persons can take more than 750 mg daily (750 mg for patients weighing 50 kg or more, 500 mg for patients weighing less than 50 kg).

Patients may find the drug more acceptable if it is administered with orange juice or milk, or after milk, or at bedtime to avoid nausea. Among patients on directly observed treatment, a daily dose of 750 mg can be given as 250 mg under strict observation and 500 mg self-administered 10-12 hours later.

ADVERSE REACTIONS

Protionamide is generally considered to be less unpleasant and better tolerated than ethionamide. But adverse reactions are essentially similar. The main troubles are epigastric discomfort, anorexia, nausea, metallic taste and sulfurous belching. Vomiting and excessive salivation can occur. Tolerance varies in different populations: the drug is usually well tolerated in Africa and Asia.

Psychotic reactions including hallucinations and depression may occur. Hypoglycaemia is a rare but dangerous occurrence, obviously particularly important in diabetic patients.

Hepatitis may occur in about 10% of cases but is rarely serious. When major liver damage occurs, jaundice and highly symptomatic disease is created, with prolonged elevation of transaminases (6-8 weeks) and drug administration should be interrupted.

Prolonged administration in large doses may produce hypothyroidism and goitre as the drug has an antithyroid effect. These will reverse when the drug is withdrawn.

Other rare side-effects have included gynaecomastia, menstrual disturbance, impotence, acne, headache and peripheral neuropathy.

PRECAUTIONS

This drug should not be administered in pregnancy as it has been shown to be teratogenic to animals. It should be very carefully monitored if given to patients with diabetes, liver disease, alcoholism or mental instability.

OFLOXACIN AND CIPROFLOXACIN

Ofloxacin and ciprofloxacin are weakly bactericidal agents of the fluoroquinolone class. Both ofloxacin and ciprofloxacin have bactericidal effects in vitro against *M. tuberculosis*. Although neither drug has been studied extensively in controlled clinical trials, Minimum Inhibitory Concentration pharmacokinetics suggests that ofloxacin may be preferable for monotherapy, along with other effective drugs.

There is no cross-resistance with other antituberculosis agents, but complete cross-resistance between ofloxacin and ciprofloxacin (and between these drugs and other fluoroquinolones such as levofloxacin) although drug resistance may be incomplete if it is low-dose resistance.

PRESENTATION AND DOSAGE

Fluoroquinolones are supplied in the form of tablets containing:

- 200 mg or 400 mg of ofloxacin
- 250 mg or 500 mg of ciprofloxacin

The usual daily dose is 600-800 mg (3-4 tablets) of ofloxacin or 1000-1500 mg (4-6 tablets) of ciprofloxacin during the initial phase. If the dose of 800 mg is poorly tolerated, the daily dose can be reduced (400 mg ofloxacin) during the continuation phase. Either can be given in a single daily dose (especially applicable in directly observed treatment) or the daily dose can be divided and given at 12-hour intervals.

ADVERSE REACTIONS

Adverse reactions are uncommon but consist of gastrointestinal disturbance (anorexia, nausea, vomiting) or central nervous system symptoms (such as dizziness, headache, mood changes and rarely convulsions).

PRECAUTIONS

These drugs should not be used in pregnant women or children because they may impair growth and produce injury to growing cartilage.

Because of drug-drug interaction, the following drugs should be avoided: antacids, iron, zinc, sucralfate.

CYCLOSERINE (OR TERIZIDONE)

Cycloserine is bacteriostatic at the usual dosage. Terizidone is a combination of two molecules of cycloserine. This antibiotic does not share cross-resistance with other drugs. It was valuable in preventing resistance to ethionamide in the re-treatment regimens (ethionamide, cycloserine, pyrazinamide or kanamycin) used before the rifampicin era. Nowadays, its value remains to prevent resistance to other reserve drugs.

PRESENTATION AND DOSAGE

The drug is given orally in tablets or capsules containing:

- 250 mg of cycloserine or
- 300 mg of terizidone.

The maximum daily dose is 15-20 mg/kg; the usual dose is 500-750 mg of cycloserine, or 600 mg of terizidone. Few patients tolerate more than 750 mg daily, or 500 mg daily in the continuation phase. The daily dose can be given in two intakes:

- cycloserine: 250 mg, in the morning, and 500 mg 12 hours later.
- terizidone: 300 mg twice a day at 12-hour intervals.

ADVERSE REACTIONS

Adverse reactions include dizziness, slurred speech, convulsions, headache, tremor, insomnia, confusion, depression and altered behaviour. The most dangerous risk is that of suicide, so mood should be carefully watched. Very rarely there may be a generalized hypersensitivity reaction or hepatitis.

PRECAUTIONS

In view of the possible adverse reactions, monitoring for central nervous system reactions is essential when cycloserine is prescribed. To prevent minor adverse reactions such as insomnia, administration of small doses of a tranquillizer is sometimes recommended. Pyridoxine may decrease central nervous system effects. The nurses in charge of treatment of inpatients and the families of outpatients should be warned to report any undue depression or personality change immediately.

Cycloserine (and terizidone) should be avoided in patients with a history of epilepsy, mental illness or alcoholism. It should be used very cautiously in patients with renal failure.

P-AMINOSALICYLIC ACID (PAS)

PAS is a bacteriostatic agent: its principal value was as an effective companion drug to isoniazid, preventing the emergence of isoniazid-resistant organisms. It was commonly used 30 years ago, but rarely nowadays.

PRESENTATION AND DOSAGE

PAS is bulky and unpleasant to take because of gastrointestinal discomfort. Two presentations are available on the market:

- Tablets, sugar-coated, containing sodium salt: sodium p-aminosalicylate, each tablet containing 0.5 g of PAS
- Granules of PAS with an acid-resistant outer coating rapidly dissolved in neutral media. Granules are supplied in packets containing 4 g per packet.

The daily dosage of the usual tablet preparation is 150 mg/kg or 10-12 g daily in two divided doses. The recommended schedule is 5 to 6 g (10 to 12 tablets) every 12 hours. The daily dosage of the granular preparation is the same. There is some

evidence that a lower dose of 4 g every 12 hours (8 g/day) of the granular preparation is associated with good blood levels and improved tolerance.

ADVERSE REACTIONS

The main adverse reactions are gastrointestinal disturbance and general skin or other hypersensitivity, including hepatic dysfunction. Hypokalaemia may also occur.

Anorexia, nausea, vomiting and abdominal discomfort are more common than diarrhoea. They may be lessened by administering the drug after food or with milk. One should not enquire of the patient how they are tolerating the drug. The patient who expects to experience nausea and vomiting is much more likely to do so. Wait until the patient complains. It may be necessary to lower the dose slightly and then increase over a few days.

Prolonged administration in large doses may produce hypothyroidism and goitre as PAS has an antithyroid effect. These will reverse when the drug is withdrawn.

PRECAUTIONS

PAS is best avoided in renal failure as it may exacerbate acidosis. The sodium salt should not be given when a restricted sodium intake is indicated. The old preparation (tablets) impaired the absorption of rifampicin, on account of an excipient (bentonite). The new preparation (granules) will not interfere with rifampicin absorption. A urine test for the drug is available (ferric chloride test).¹

¹ Horne NW, ed. Modern drug treatment of tuberculosis, 7th ed. London, Chest, Heart and Stroke Association, 1990.

ANNEX 4

EXAMPLES OF NUMBER OF TABLETS OF ANTITUBERCULOSIS DRUGS FOR TREATMENT ACCORDING TO WEIGHT BANDS

Table 1 Sample regimens (Category I) with separate antituberculosis drugs in adults^a

	WEIGHT IN KG			
	30-39	40-54	55-70	>70
Initial phase - daily				
H 100 mg	1.5	2.5	3	3.5
R 150 mg	2	3	4	5
Z 400 mg	2	3	4	5
E 400 mg	1.5	2	3	3.5
Continuation phase - daily				
either H 100 mg	1.5	2.5	3	3.5
R 150 mg	2	3	4	5
or H 100 mg	1.5	2.5	3	3.5
E 400 mg	1.5	2	3	3.5
Continuation phase - 3 times weekly				
H 300 mg	1	1.5	2	2.5
R 150 mg	2	3	4	5

^a Adapted from *Guidelines for tuberculosis treatment in adults and children in national tuberculosis programmes*. Geneva, World Health Organization, 1991 (document WHO/TUB/91.161); and *Management of tuberculosis: a guide for low income countries*, 5th ed. Paris, International Union Against Tuberculosis and Lung Disease, 2000.

Table 2 Sample regimens with fixed-dose combinations of antituberculosis drugs in adults^a

	WEIGHT IN KG			
	30-39	40-54	55-70	>70
Initial phase - daily				
HRZE (75 mg + 150 mg + 400 mg + 275 mg)	2	3	4	5
or: HRZ (75 mg + 150 mg + 400 mg)	2	3	4	5
Category II: add S (vial 1 g) for 2 months	0.5	0.75	1	1
Continuation phase - daily				
either HR (75 mg + 150 mg)	2	3	4	5
Category II: add E (400 mg)	1.5	2	3	3
or HE (150 mg + 400 mg)	1.5	2	3	3
Continuation phase - 3 times weekly				
HR (150 mg + 150 mg)	2	3	4	5
Category II: add E 400 mg	2	4	6	6

^a Adapted from Blomberg B et al. *Informal consultation on 4-drug fixed-dose combinations compliant with the WHO model list of essential drugs*, Geneva, 15–17 August 2002. Geneva, World Health Organization (unpublished).

Table 3 Sample regimens (Category I) with separate antituberculosis drugs in children^a

	WEIGHT IN KG		
	5-10	11-20	21-30
Initial phase - daily			
H 100 mg	1/2	1	2
R 150 mg	1/2	1	2
Z 400 mg	1/2	1	2
E 400 mg	-	-	1
S 1 g (in TB meningitis)	0.25	0.33	0.5
Continuation phase - daily			
H 100 mg	1/2	1	2
R 150 mg	1/2	1	2
Continuation phase - 3 times weekly			
H 100 mg	1	1 1/2	3
R 150 mg	1/2	1	2

^a Adapted from *Guidelines for tuberculosis treatment in adults and children in national tuberculosis programmes*. Geneva, World Health Organization, 1991 (document WHO/TUB/91.161).

Table 4 Sample regimens with fixed-dose combinations of antituberculosis drugs in children (paediatric formulations)^a

	WEIGHT IN KG					
	UP TO 7	8-9	10-14	15-19	20-24	25-29
Initial phase - daily						
HRZ (30 mg + 60 mg + 150 mg)	1	1 1/2	2	3	4	5
E 400mg	-	-	-	-	1	1
S 1 g	0.25	0.25	0.25	0.33	0.50	0.50
Continuation phase - daily						
HR (30 mg + 60 mg)	1	1 1/2	2	3	4	5
Continuation phase - 3 times weekly						
HR (60 mg + 60 mg)	1	1 1/2	2	3	4	5

^a Adapted from Blomberg B et al. *Informal consultation on 4-drug fixed-dose combinations compliant with the WHO model list of essential drugs*, Geneva, 15–17 August 2002. Geneva, World Health Organization (unpublished).

REFERENCE PRICE LIST OF ESSENTIAL ANTITUBERCULOSIS DRUGS

DRUG ^a	DOSAGE FORM/STRENGTH		QUANTITY	MSH PRICE INDICATOR GUIDE (US\$) ^b	GDF PRICE (US\$) ^c
Isoniazid	Tablet	100 mg	1 000	3.30	-
		300 mg	1 000	7.00	3.65 (loose)
			672	-	3.76 (blister)
Rifampicin	Tablet or capsule	150 mg	1 000	27.70	-
		300 mg	1 000	50.60	-
Pyrazinamide	Tablet	400 mg	1 000	20.80	12.64 (loose)
			672	-	9.81 (blister)
		500 mg	1000	26.50	-
Ethambutol	Tablet	400 mg	1 000	19.30	10.92 (loose)
			672	-	8.67 (blister)
Isoniazid + rifampicin	Tablet	100 mg + 150 mg	1000	21.60	11.66 (loose)
			672	-	8.87 (blister)
		150 mg + 300 mg		45.50	21.40 (loose)
		150 mg + 400 mg	1000	22.20	11.77 (loose)
Isoniazid + rifampicin + pyrazinamide + ethambutol	Tablet		672	-	8.92 (blister)
		75 mg + 150 mg + 400 mg + 275 mg	1 000		30.50 (loose)
			672		22.00 (blister)
Isoniazid + thiocetazone	Tablet	100 mg + 50 mg	1 000	4.30	-
		300 mg + 150 mg		9.30	-
Strptomycin	Powder for injection	1 g base in vial	100	7.41	-
		0.75 g base in vial	100	-	2.70
Water for injection		5 ml in vial	100	2.46	1.75

See notes on pag.108

- ^a Essential medicines: WHO model list (revised April 2002), 12th ed. Geneva, World Health Organization, 2002.
- ^b Median price as per McFadyen JE, ed. *International drug price indicator guide*. Boston, MA, Management Sciences for Health (MSH) in collaboration with the World Health Organization; updated annually. MSH Center for Pharmaceutical Management, 4301 North Fairfax Dr, Suite 400, Arlington VA 22203-1627, USA. Fax 1(703) 524-7898. E-mail cpm@msh.org. Website: <http://http://www.msh.org>.
- ^c Prices available from the Global Drug Facility at September 2002 (www.globaldrugfacility.org).
The GDF is a mechanism to expand access to, and availability of, high-quality antituberculosis drugs to facilitate global DOTS expansion. The GDF will enable governments and NGOs to implement effective TB control programmes based on the DOTS strategy. By securing the timely supply of quality antituberculosis drugs, the GDF will complement other activities designed to improve coverage and quality of global TB control. The GDF is hosted by WHO and managed by the Stop TB secretariat. In the relatively short period that the GDF has been functional, it has already had a significant impact on drug prices, with a 6-month course of daily treatment now costing less than US\$ 10 - one-third lower than previous international prices.
The GDF offers the following services: a granting mechanism for antituberculosis drugs and diagnostics; a direct procurement mechanism for countries or donors wishing to use their own resources to purchase drugs at concessionary prices; an online WEBBUY system for (1) GDF to electronically place order requests for grantees (2) grantees to track and trace their TB drug consignments (3) purchasers eligible to use the GDF Direct Procurement Mechanism to order and trace their TB drug consignments through the Internet; and a White List of products and manufacturers for countries wishing to use their own procurement mechanisms and resources (www.stoptb.unwebbuy.org).

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